Laboratiry of Mathematical Chemistry
Bourgas University, Bulgaria

Using CATABOL to predict persistency, biodegradation pathways and stable degradants

International Science Forum, *Computational Toxicology*

US EPA, May 21-23, 2007

Outlook

•QSAR and Complexity of Chemical Structure

•Toxicity as a result of metabolic activation

•Metabolism logic

•Probabilistic approach to modeling metabolism

•CATABOL for simulating microbial degradation

•Performance and reliability of predicted metabolites

•Biodegradation kinetic models

•Simulating the effect of gene modification on metabolism

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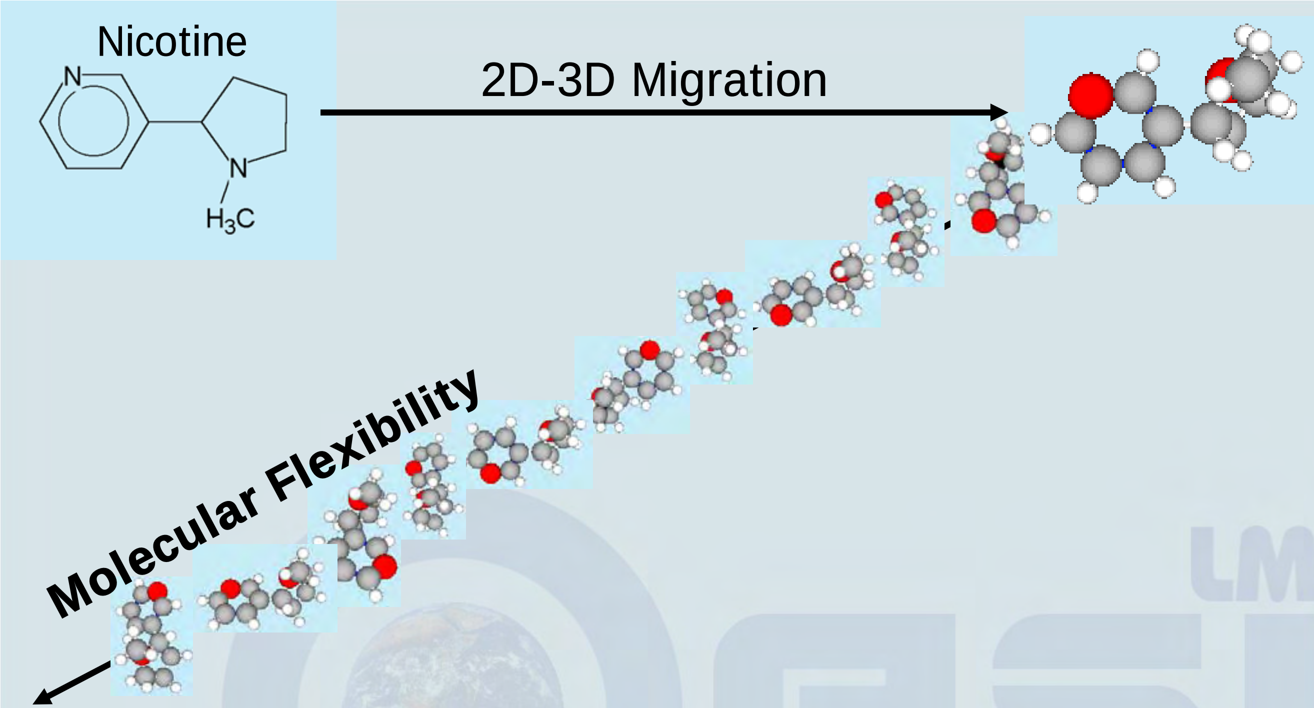
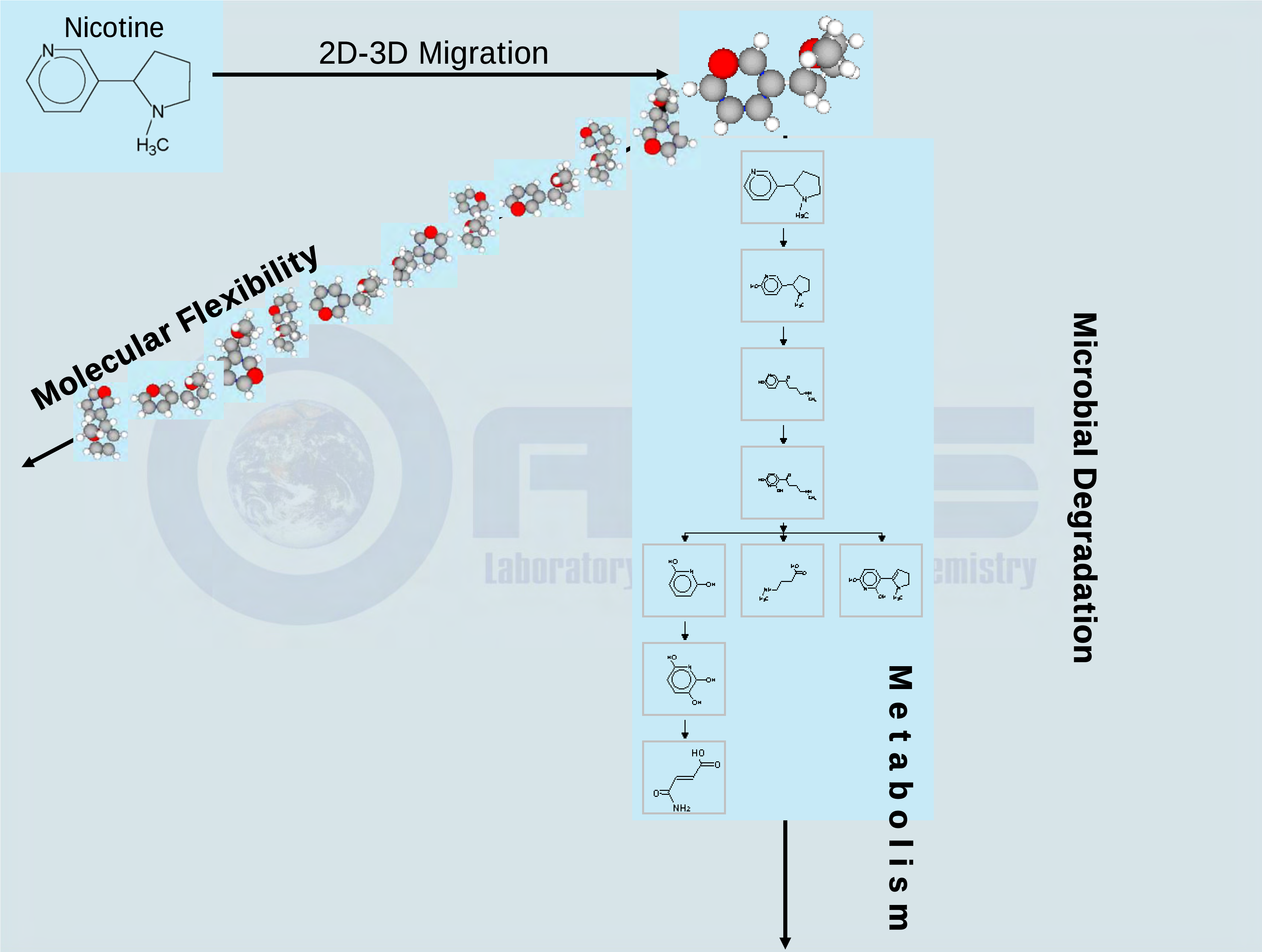
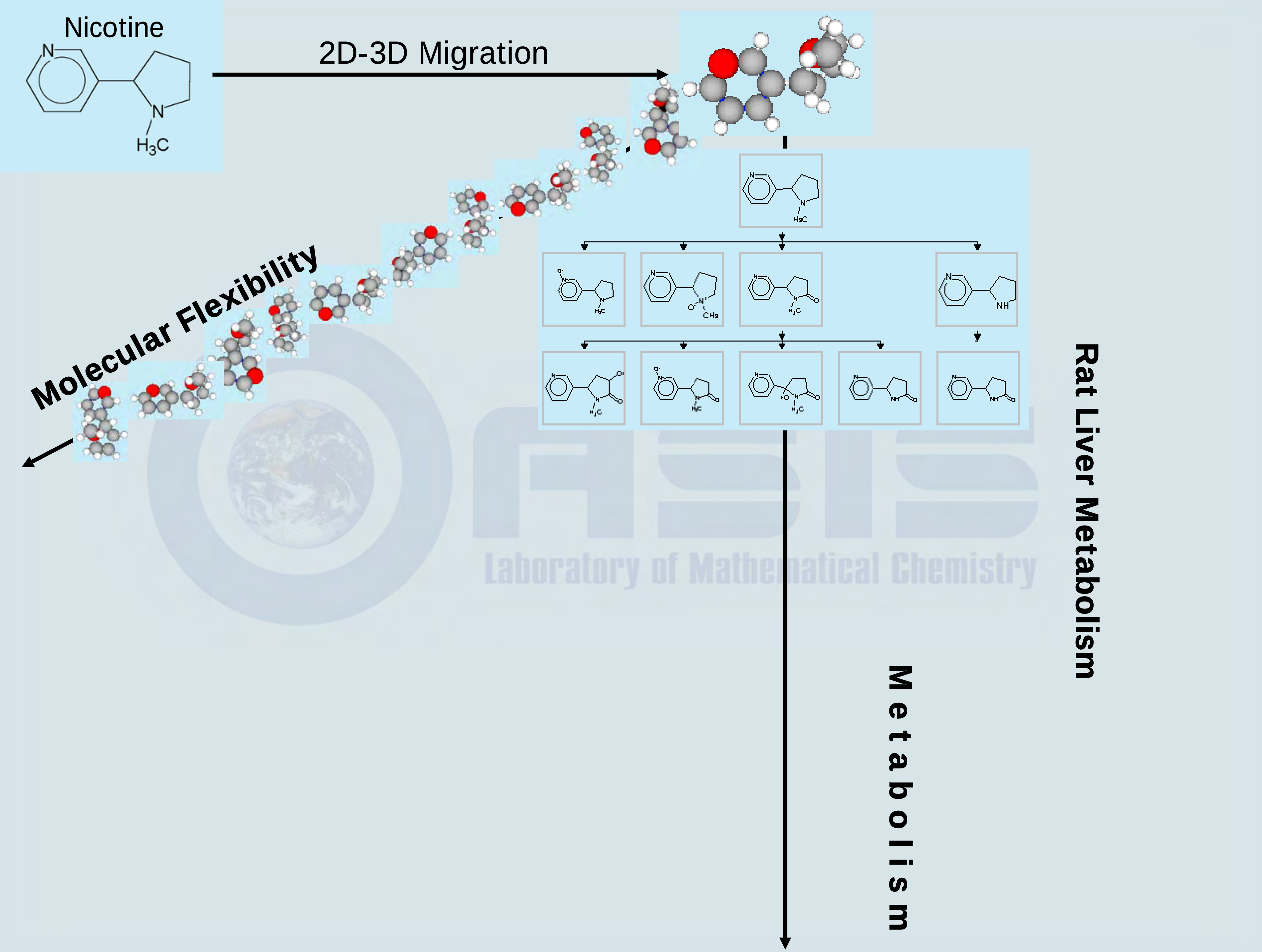
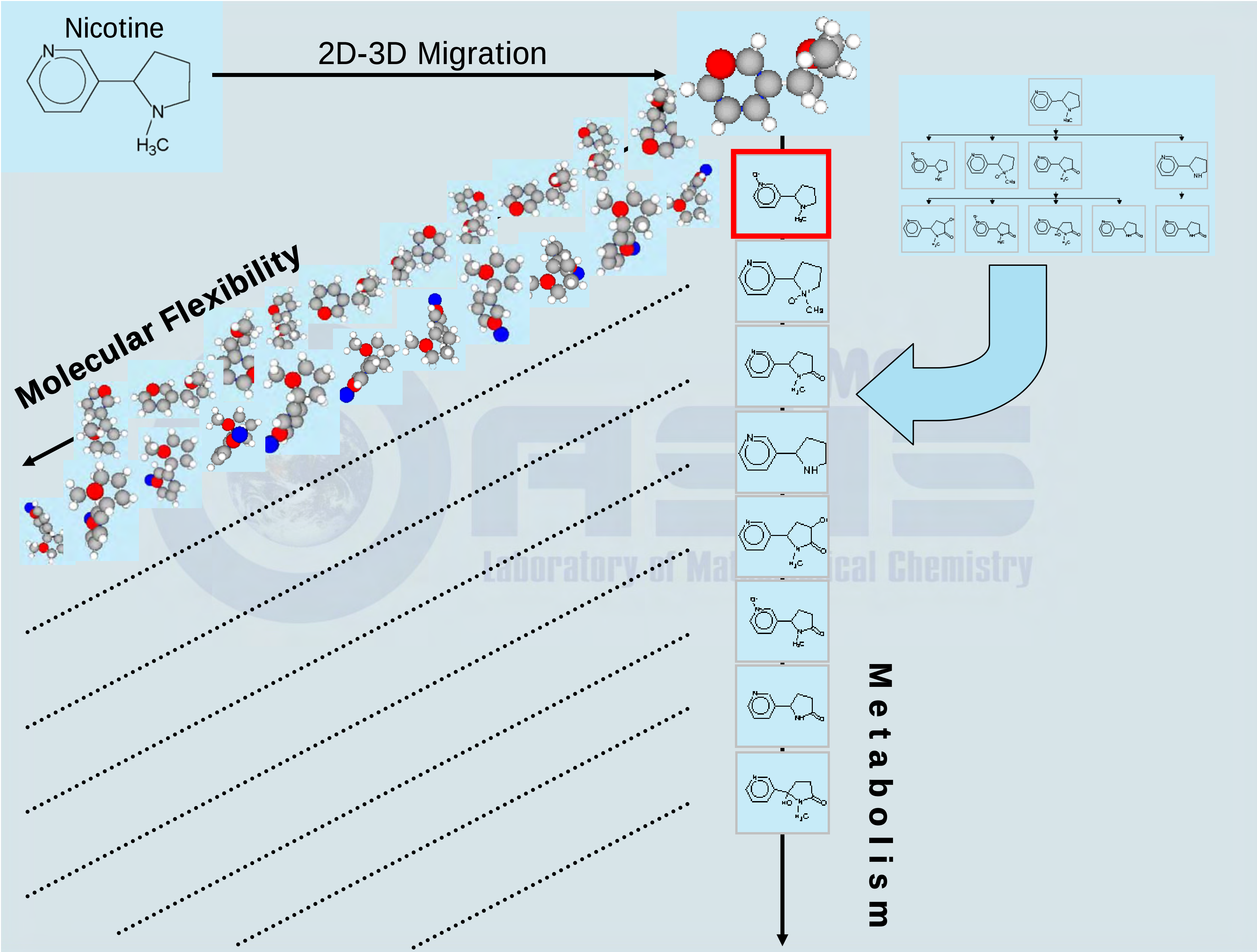

Nicotine
N
N
H3C
2D-3D Migration
Molecular Flexibility



Nicotine
2D-3D Migration
Molecular Flexibility
Microbial Degradation
Metabolism


Nicotine
2D-3D Migration
Molecular Flexibility
Rat Liver Metabolism
M e t a b o l i s m
Laboratory of Mathematical Chemistry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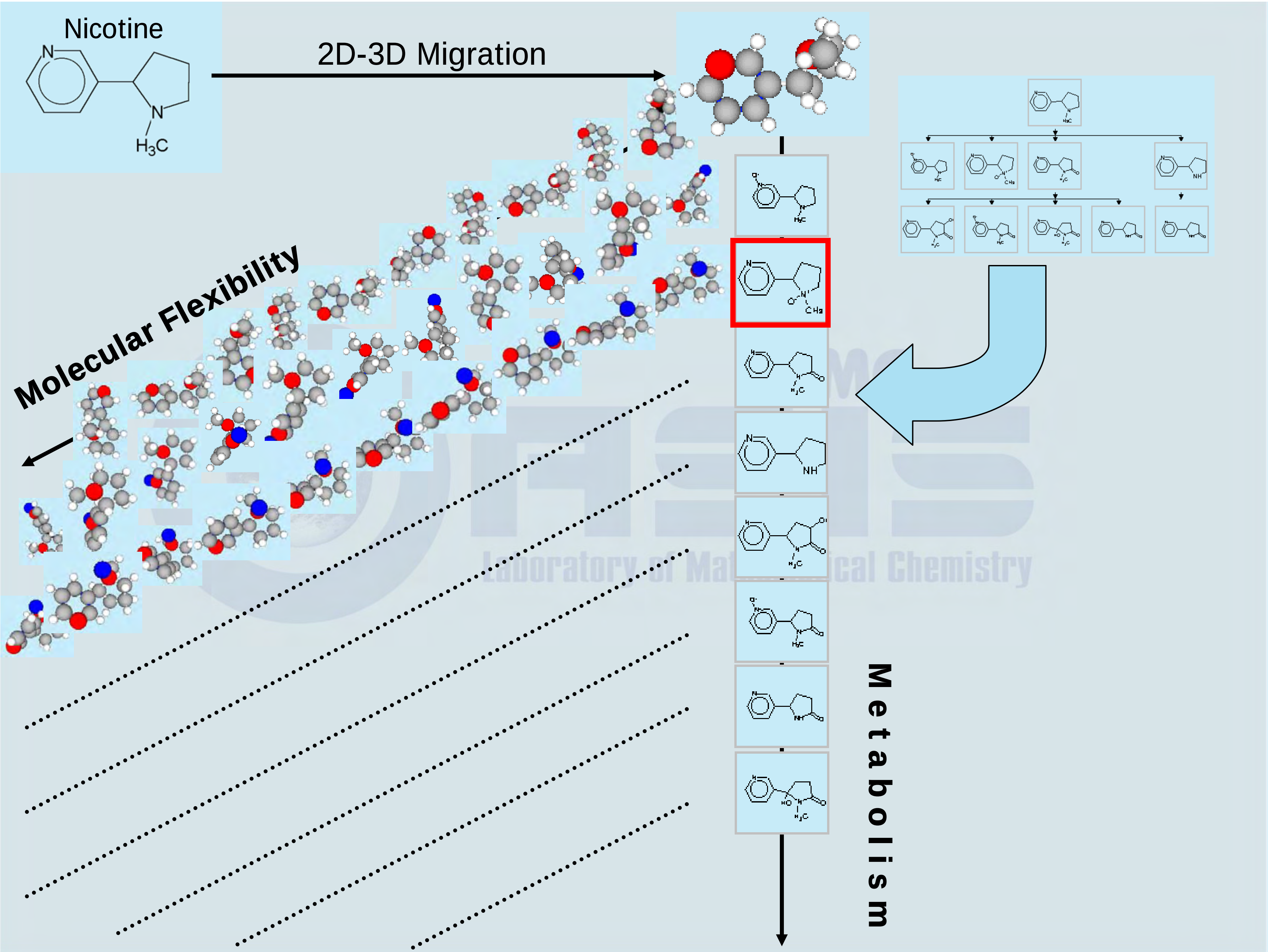

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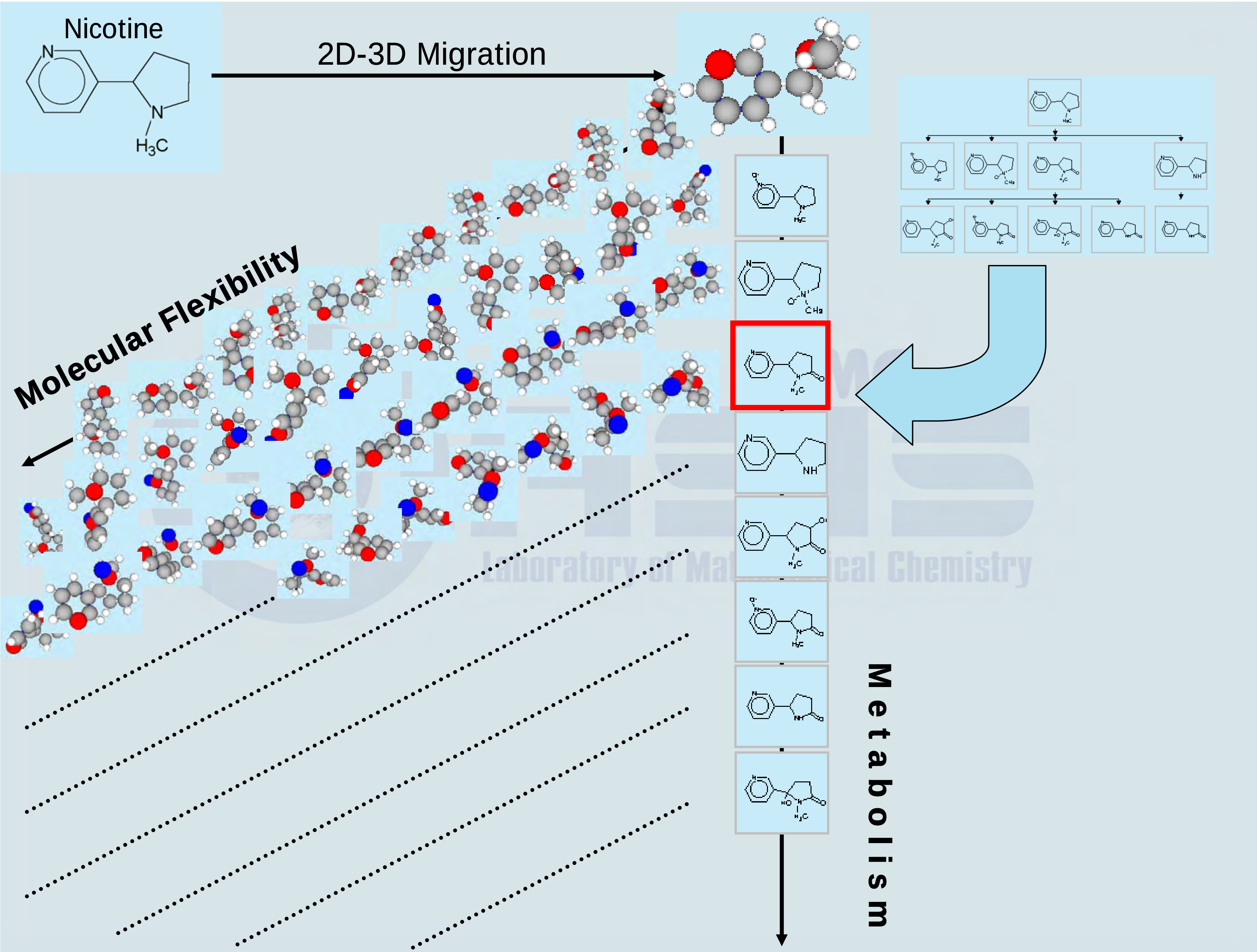
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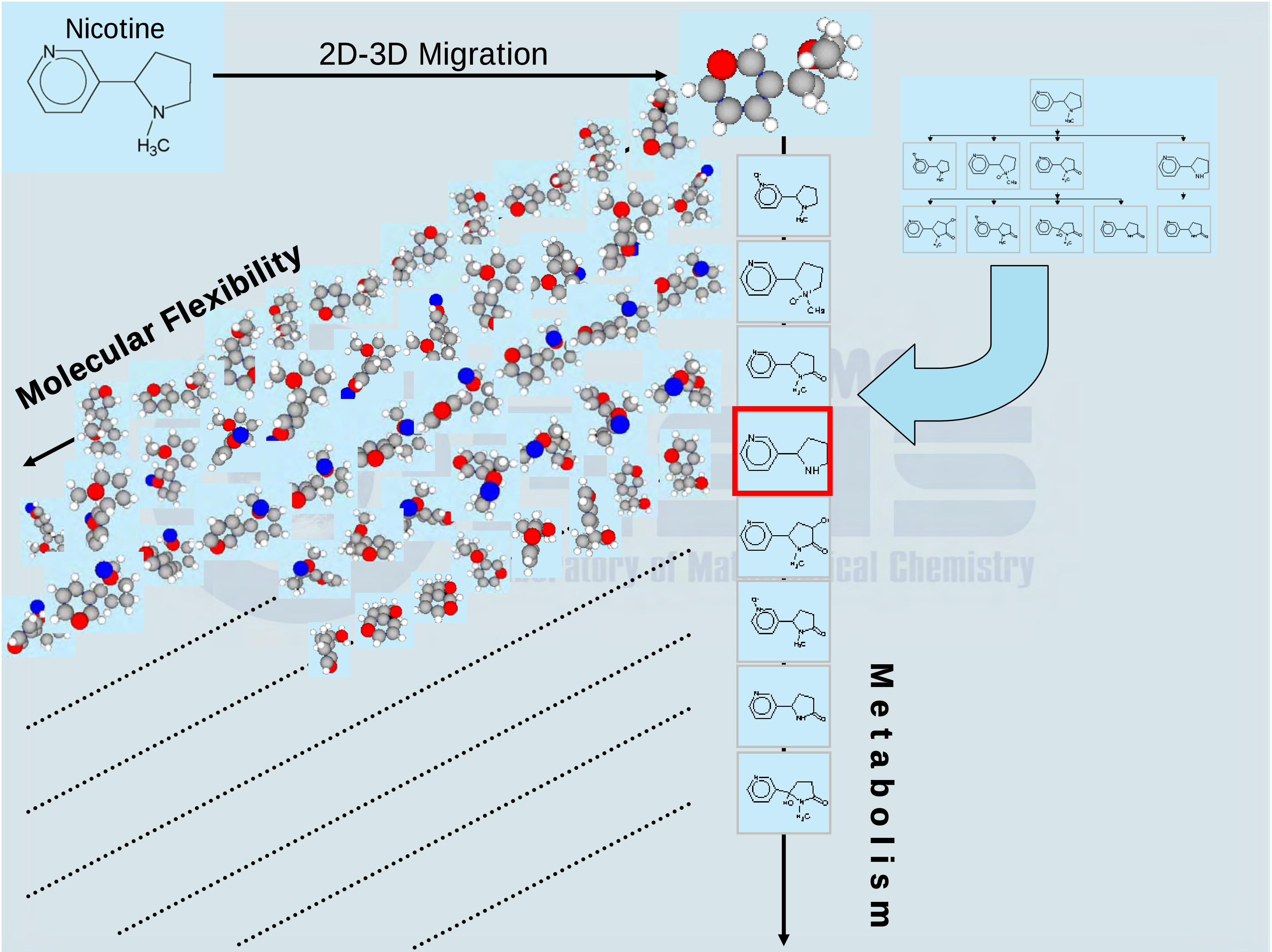
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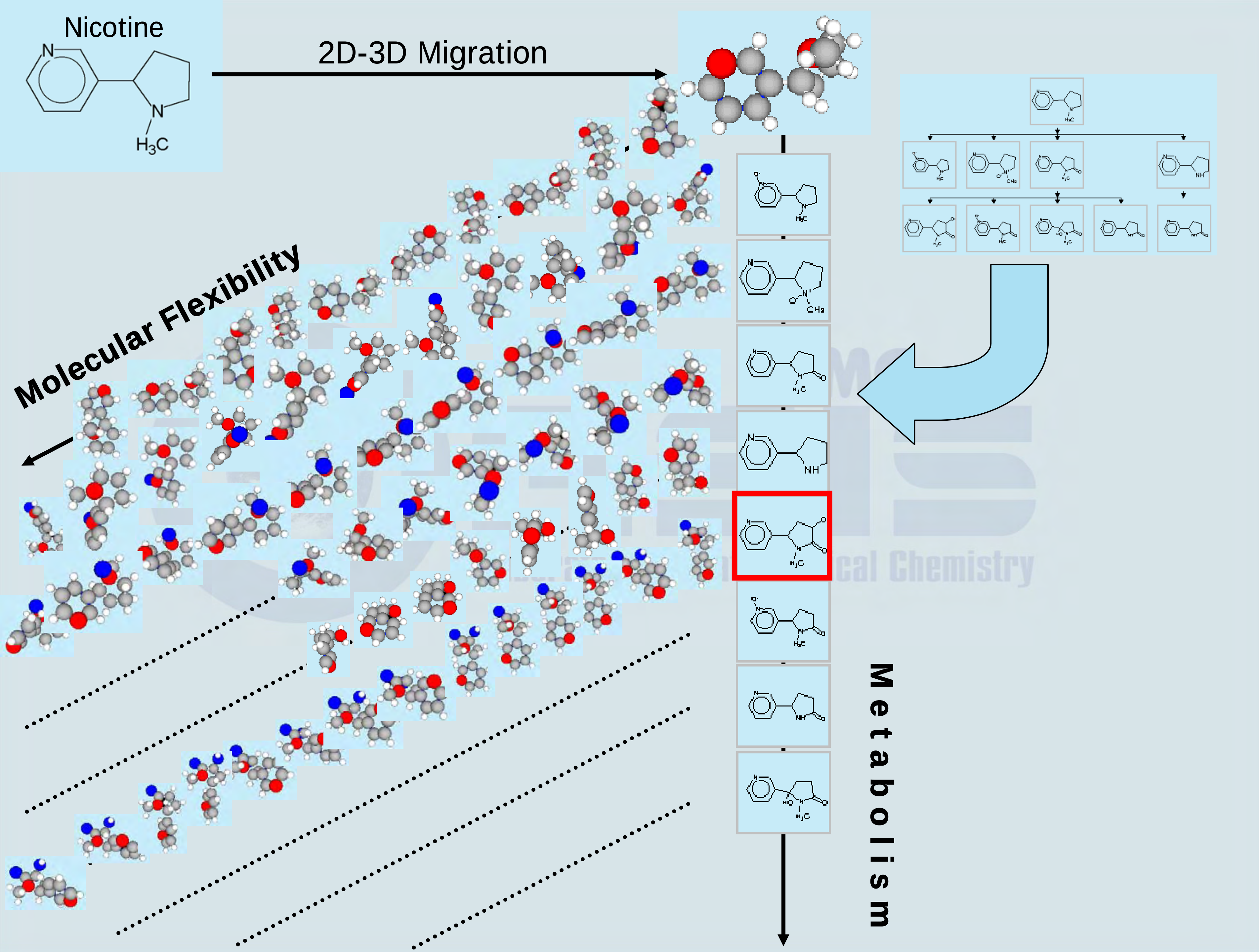

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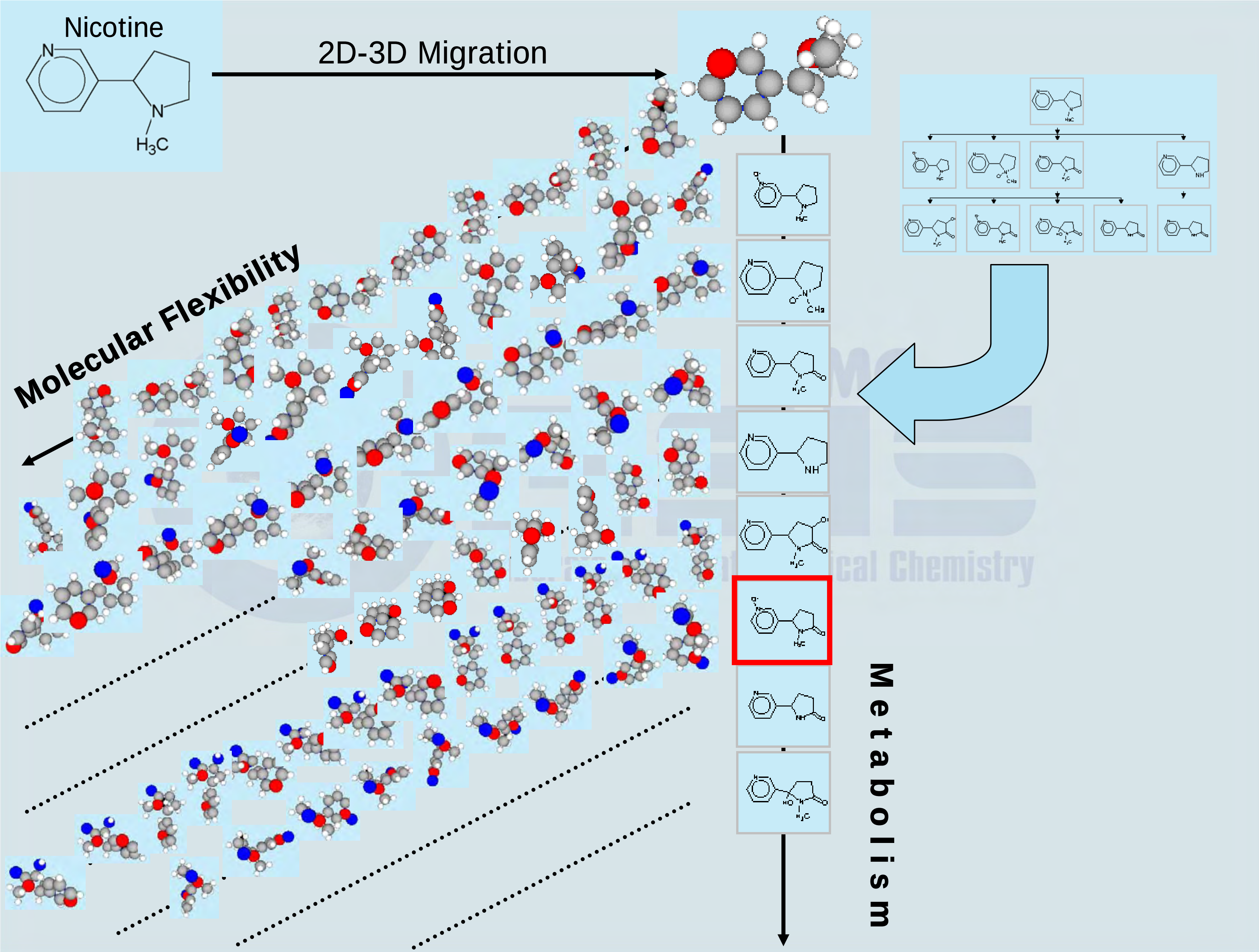
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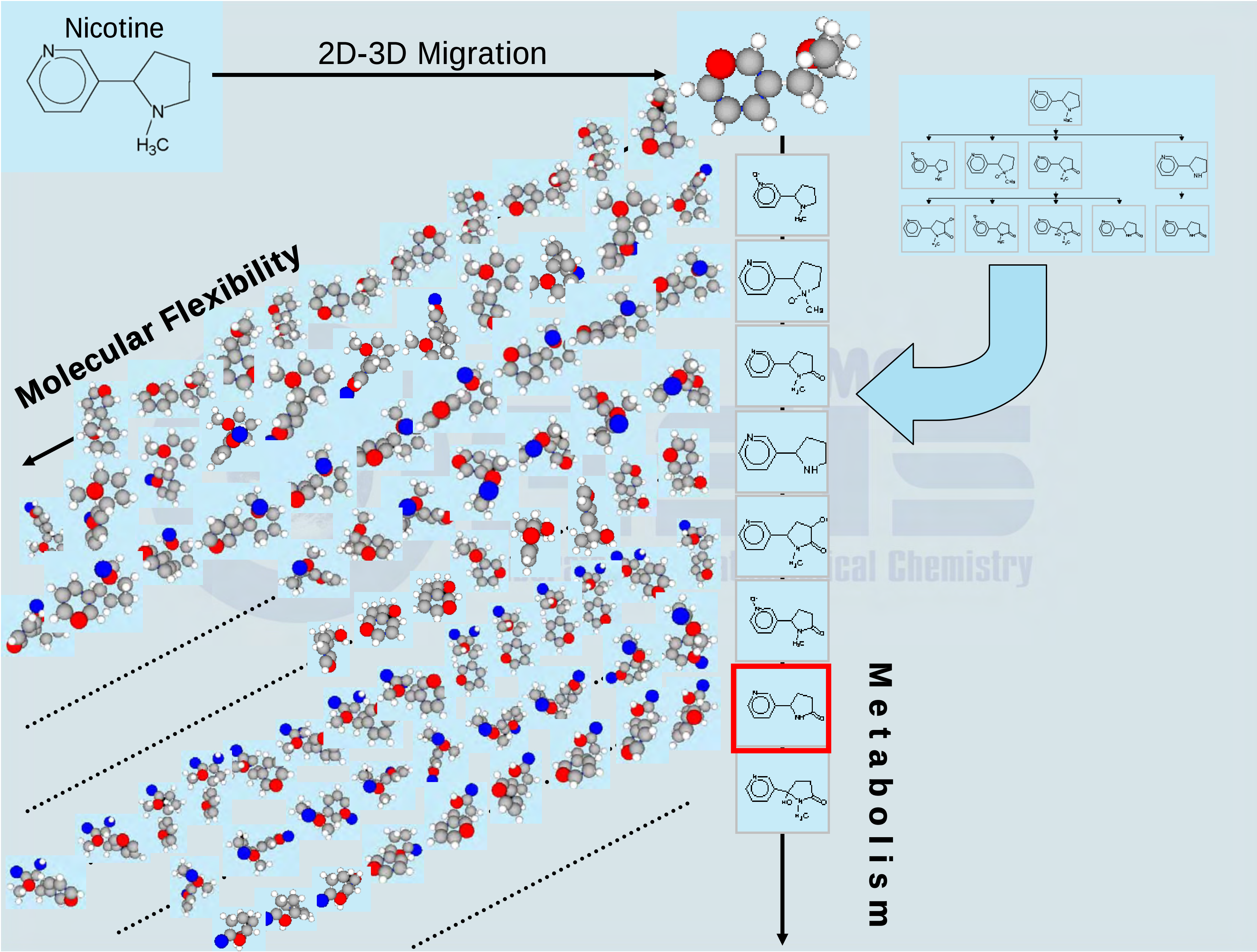

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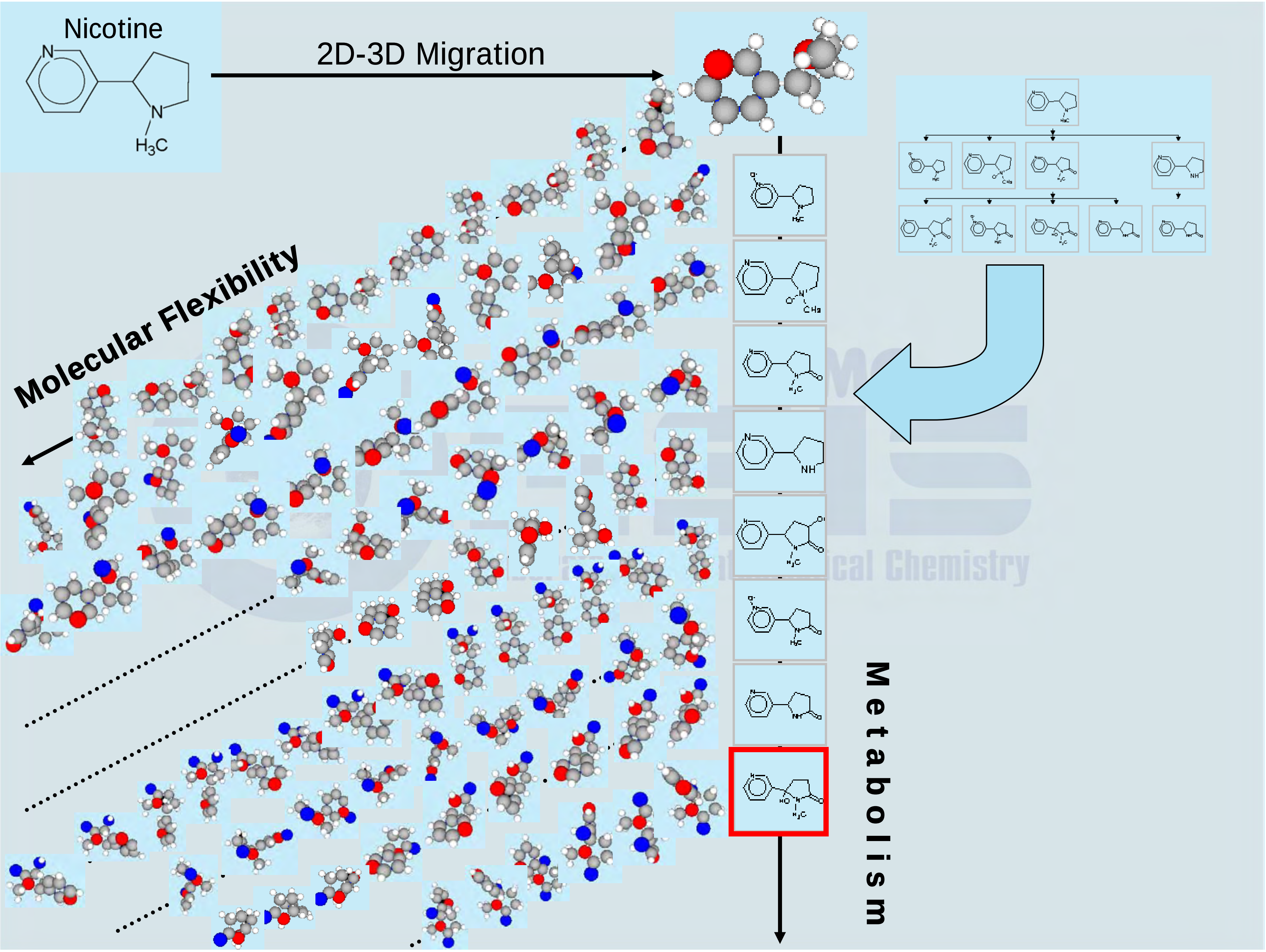
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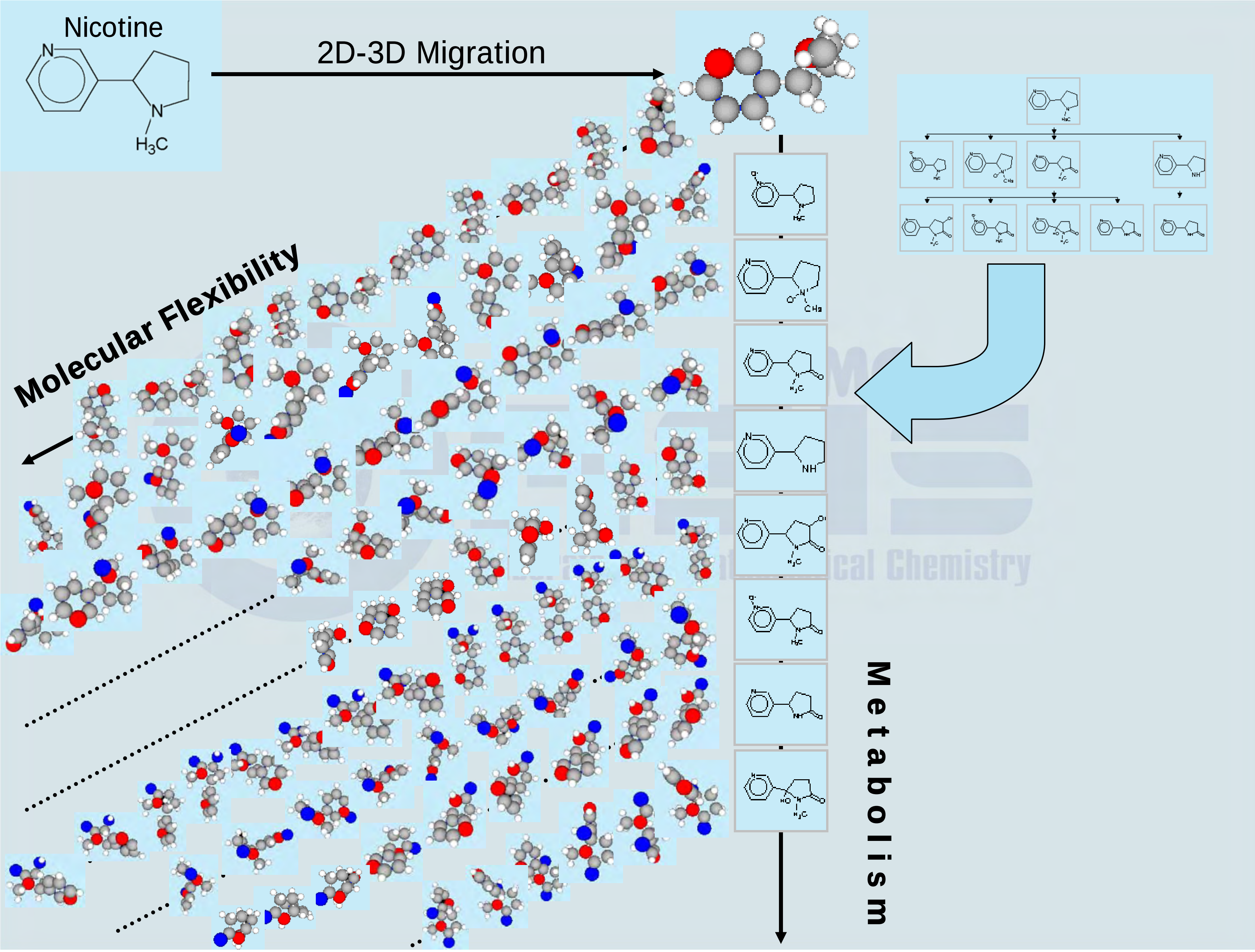

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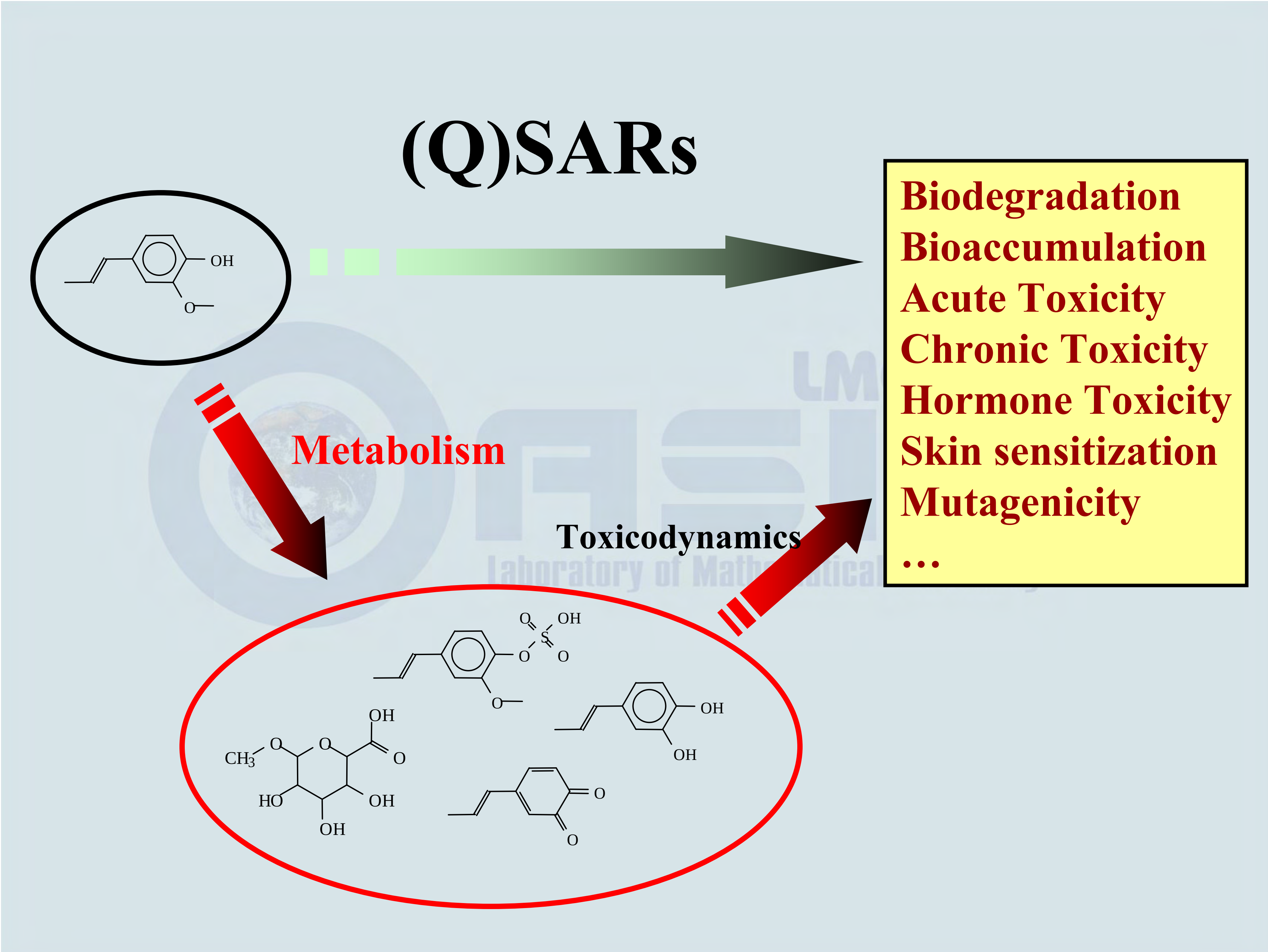
(Q)SARs
Metabolism
Toxicodynamics
Biodegradation
Bioaccumulation
Acute Toxicity
Chronic Toxicity
Hormone Toxicity
Skin sensitization
Mutagenicity
…

The OASIS QSAR Concept :

To analyze toxicity as a result of metabolic activation

Combining on same modeling platform:

- **Toxicokinetics – specific metabolism**
- **Toxicodynamic – interaction with macromolecules**

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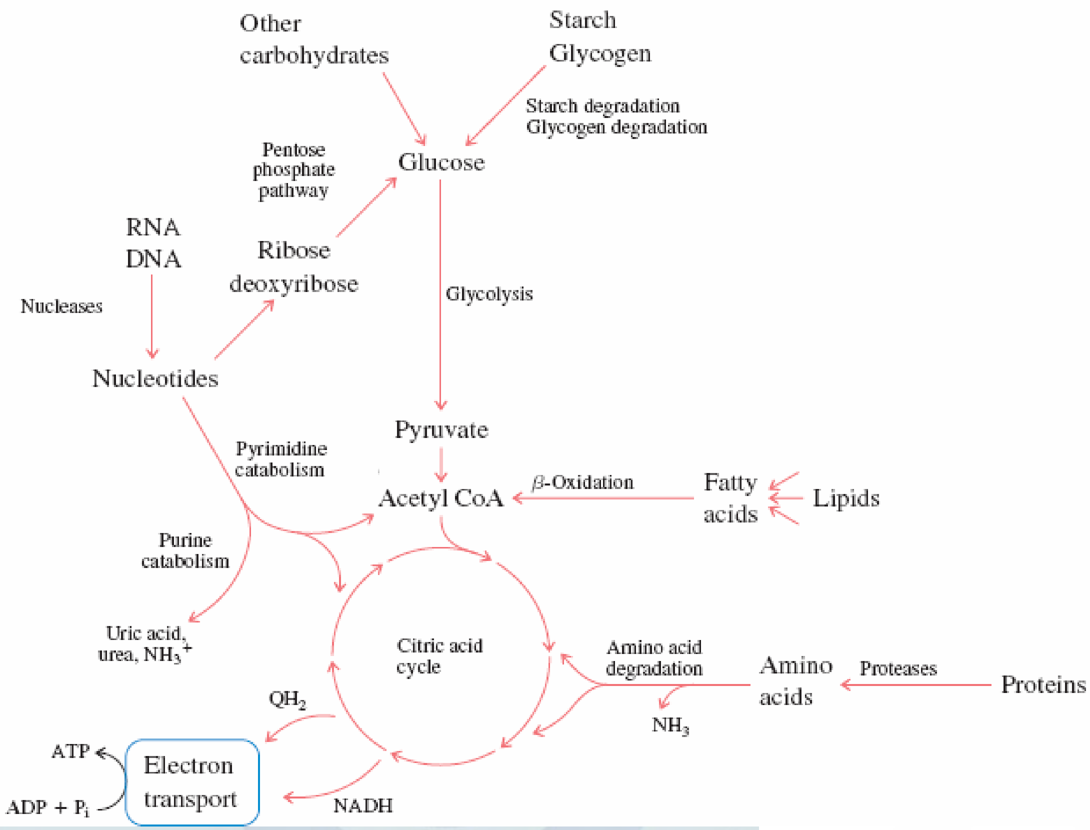
Metabolism

Energy-generating component: Catabolism

Produce energy (as ATP) and simple oxidized compounds

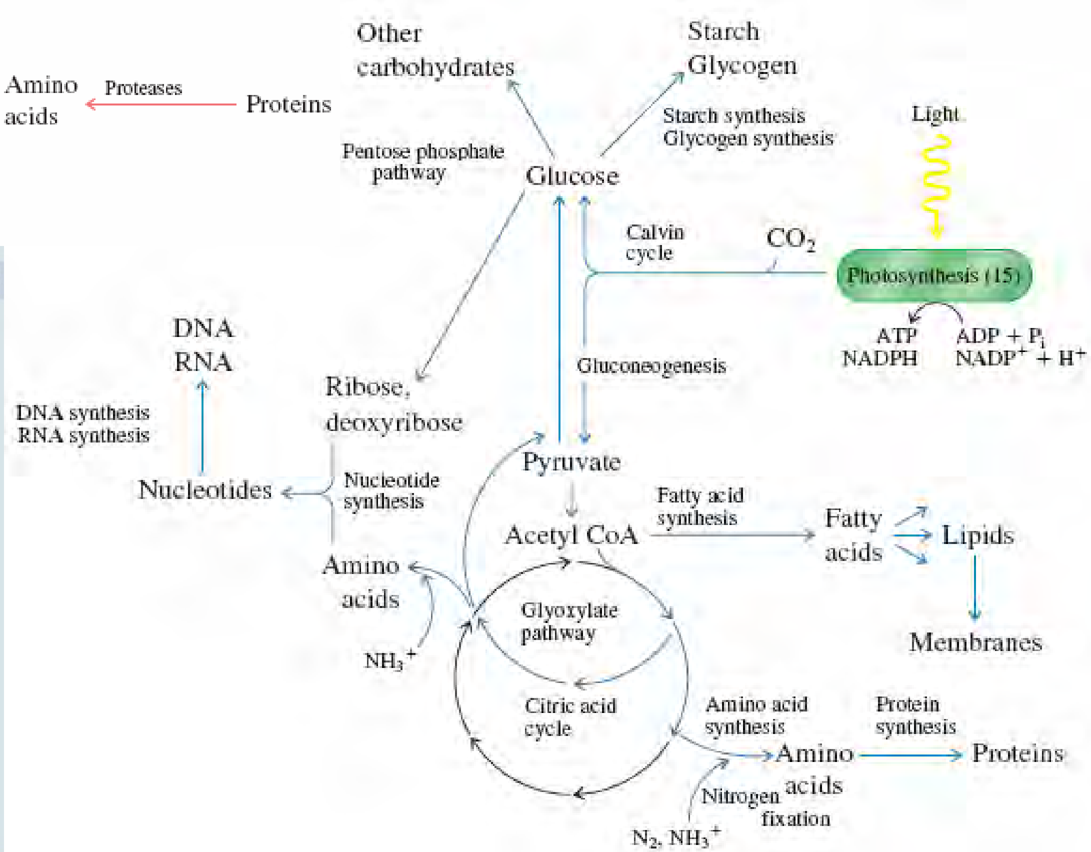
Energy-consuming component: Anabolism

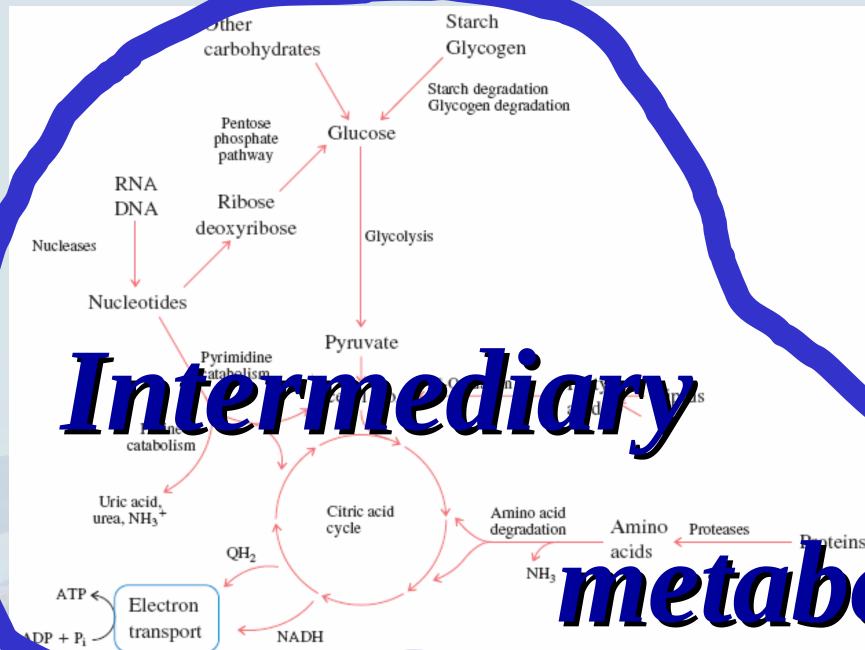
Build cell material



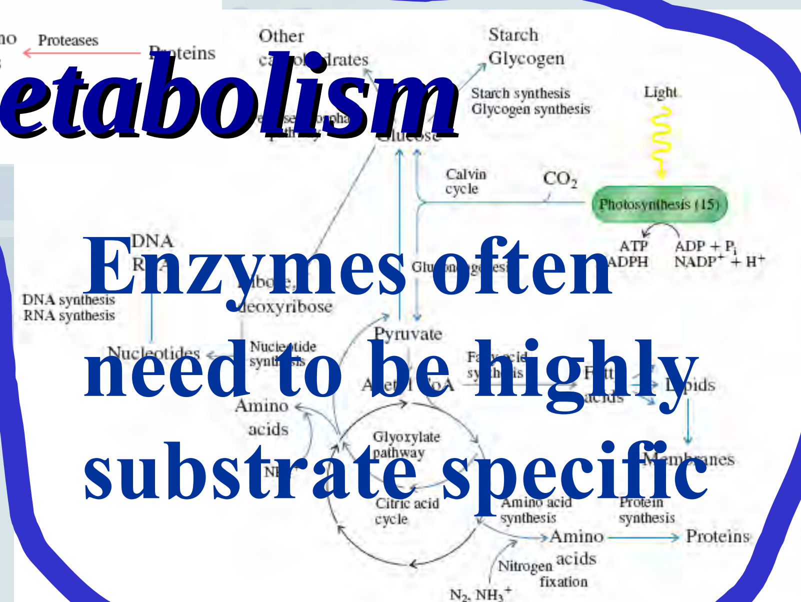
Catabolism

Anabolism





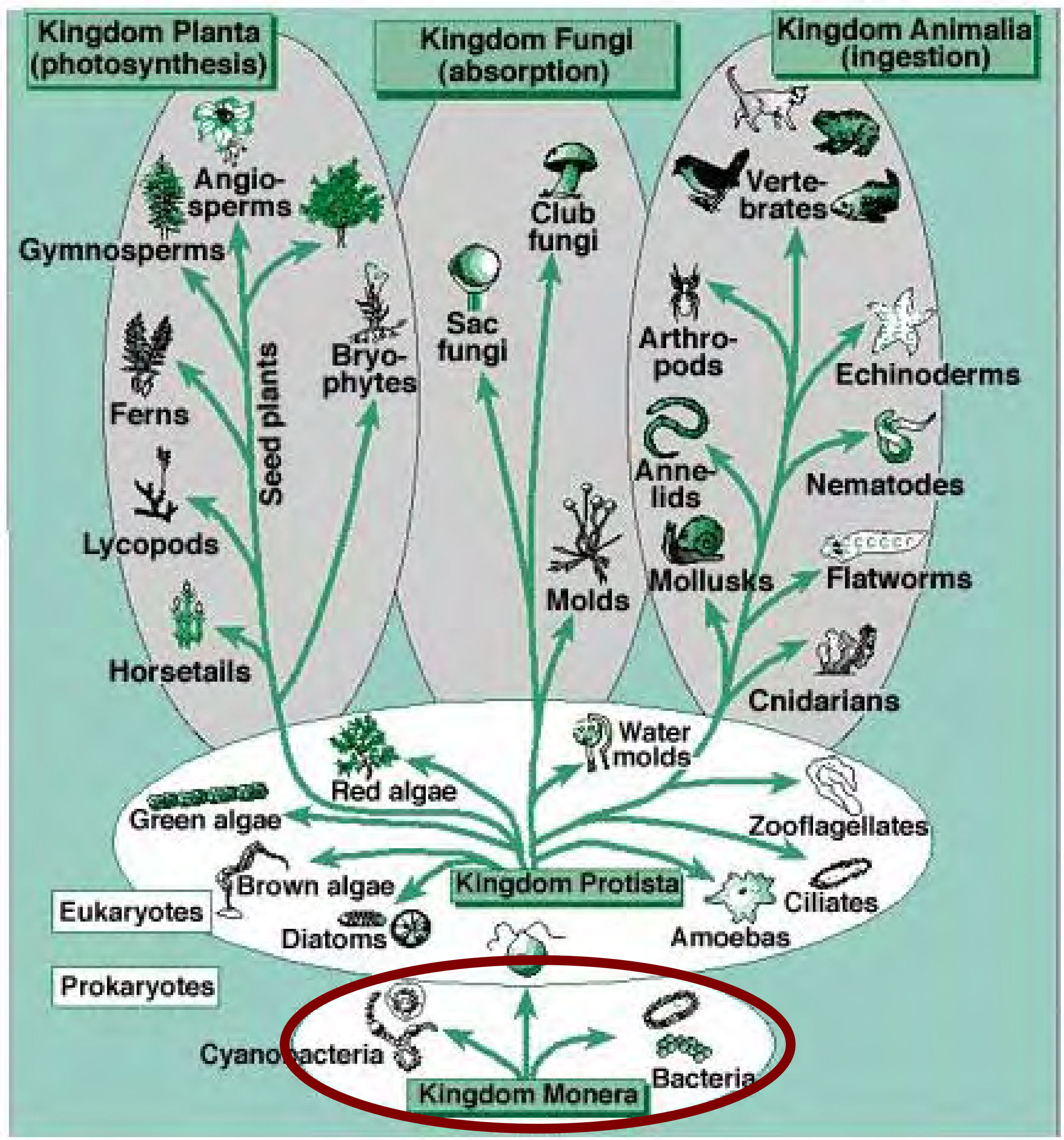
Intermediary metabolism



Enzymes often need to be highly substrate specific

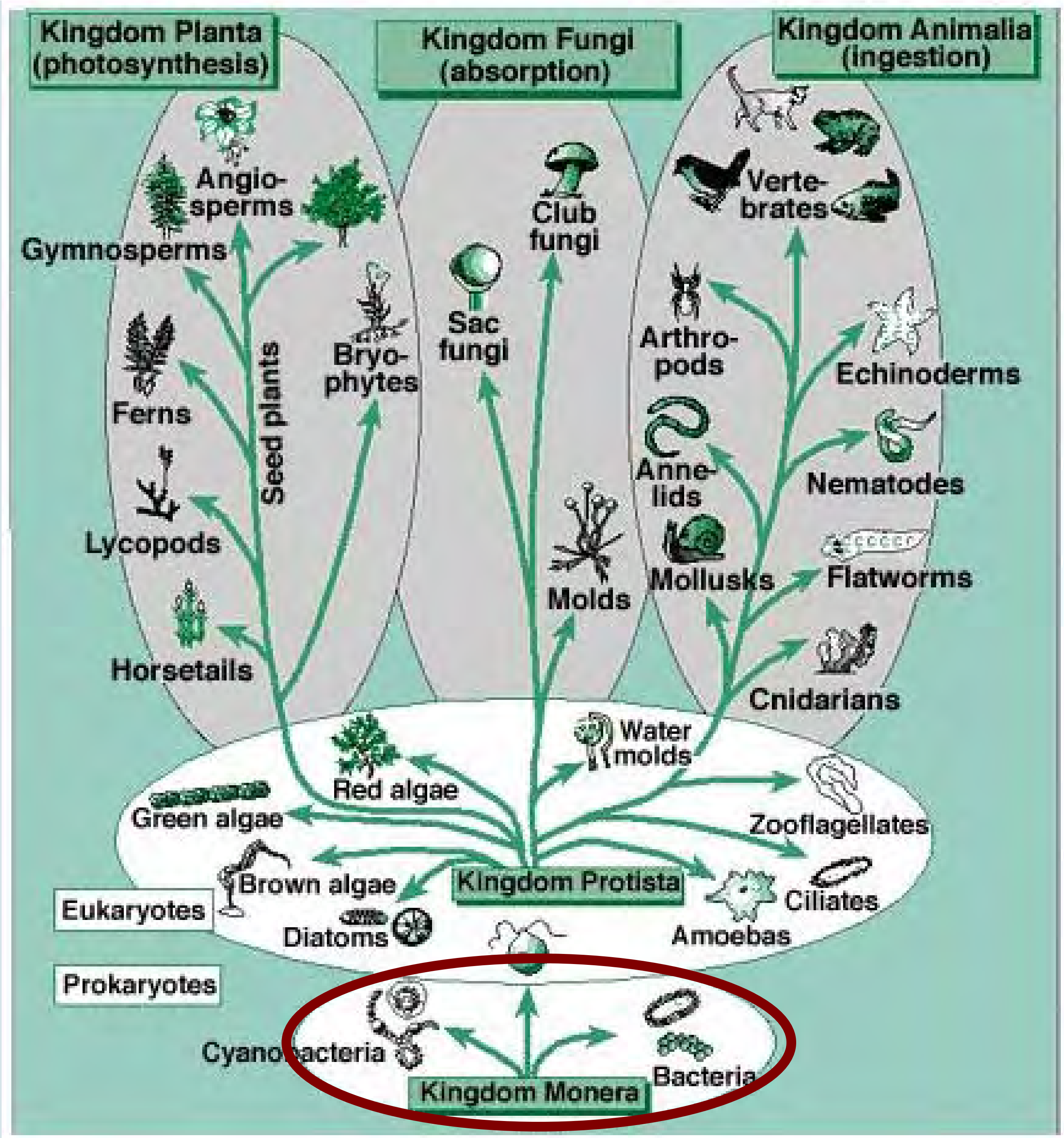
Non-intermediary metabolism

1. **Response to environment**
2. **Response to human health**



Prokaryotes

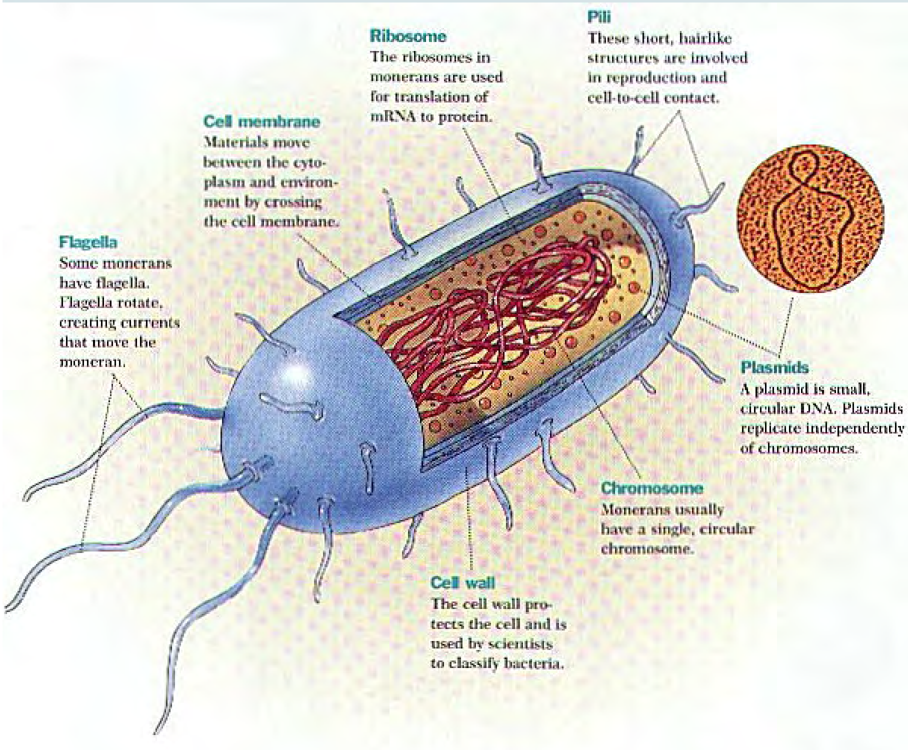
Kingdom Monera



Prokaryotes

Kingdom Monera

The Kingdom Monera (Prokaryotes)

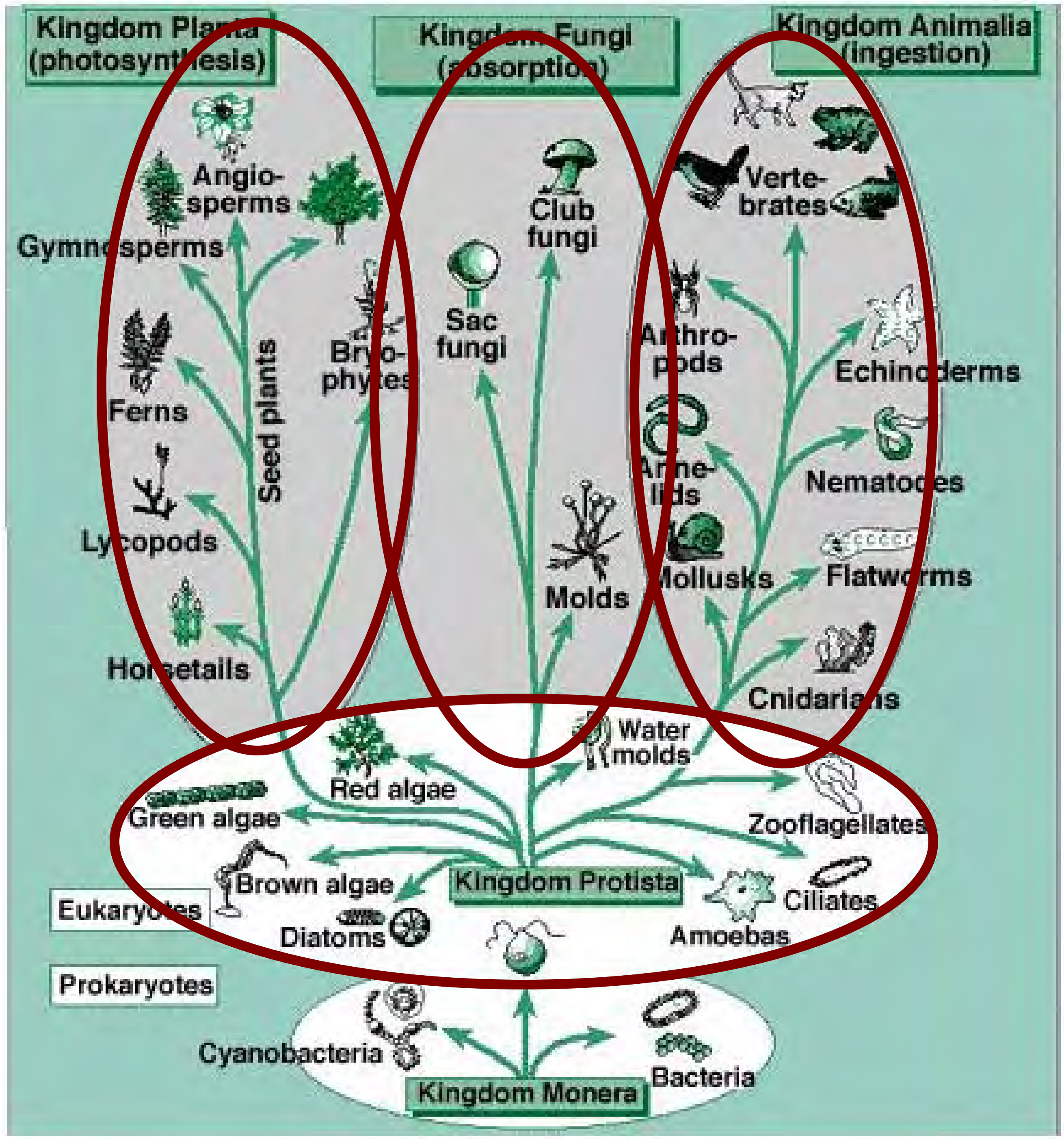


Bacteria tend to group genes that are functionally related together on the chromosome.

Operon - grouping of genes in bacteria under the control of the same regulatory system.

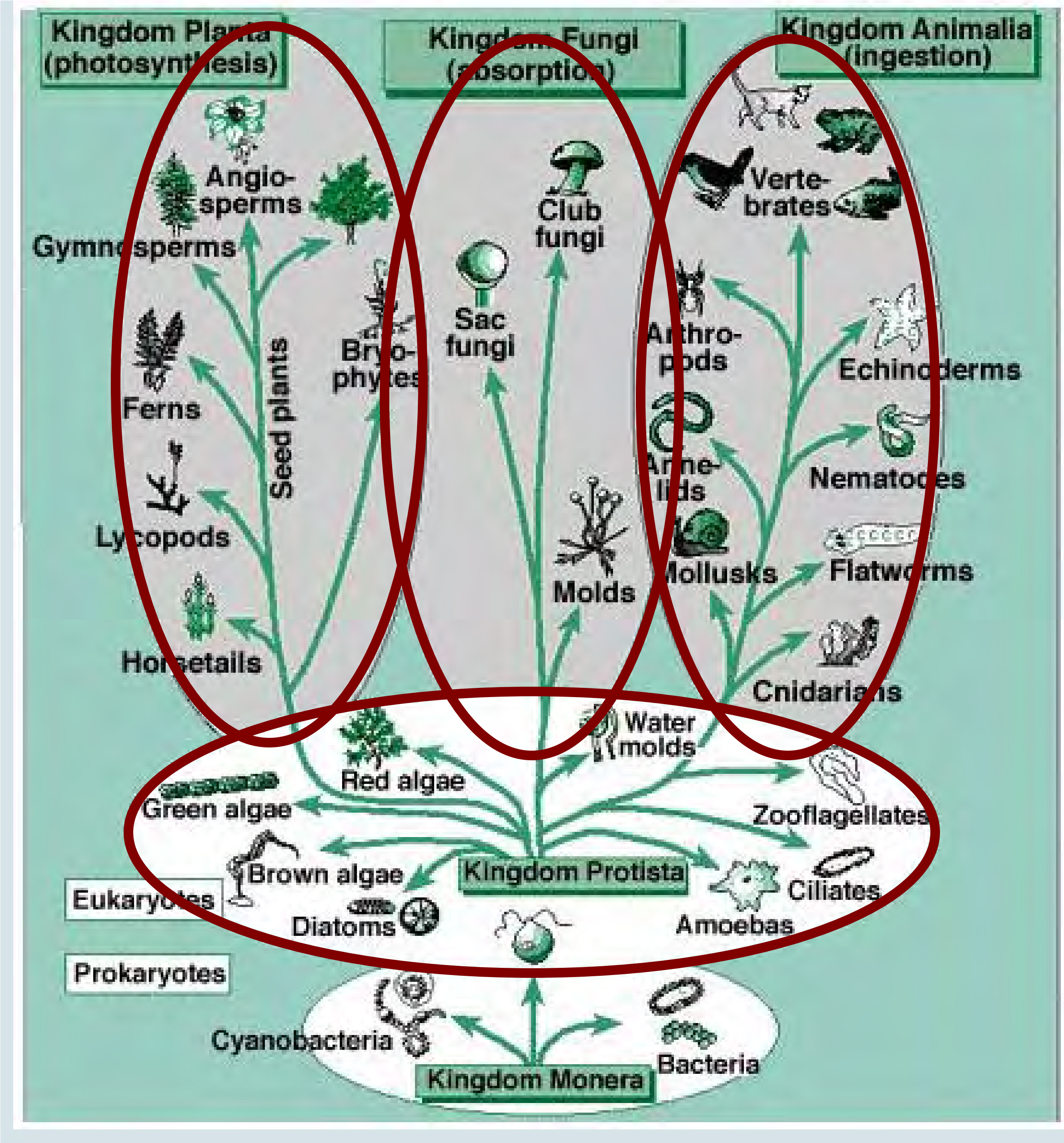
Control mechanism	**Structural gene for β-galactosidase**	**Structural gene for β-galactoside permease**	**Structural gene for β-galactoside transacetylase**

Lactose operon: contains genes that encode enzymes responsible for lactose metabolism



Eukaryotes

Kingdoms:
Protista
Planta
Fungi
Animalia



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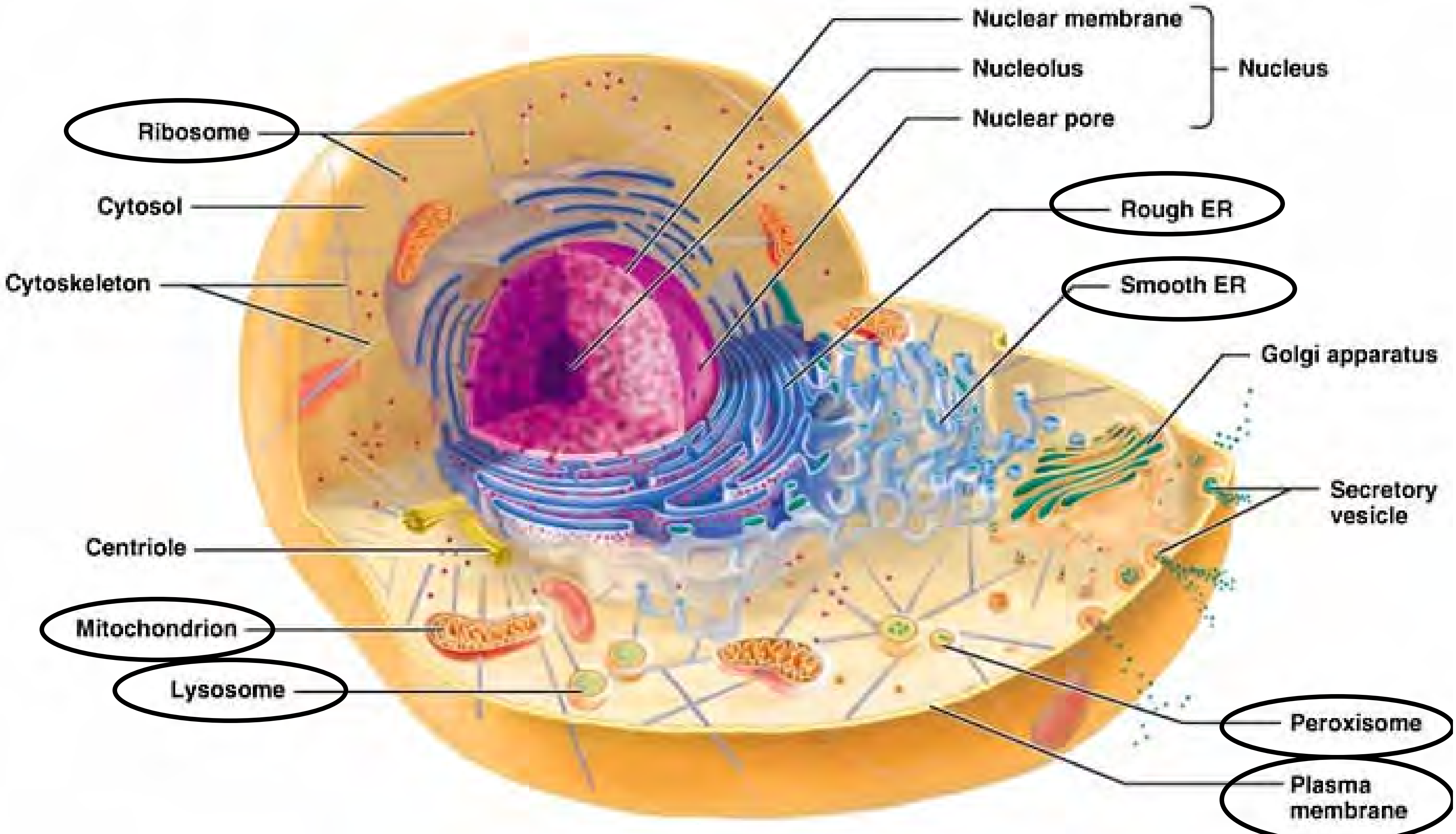
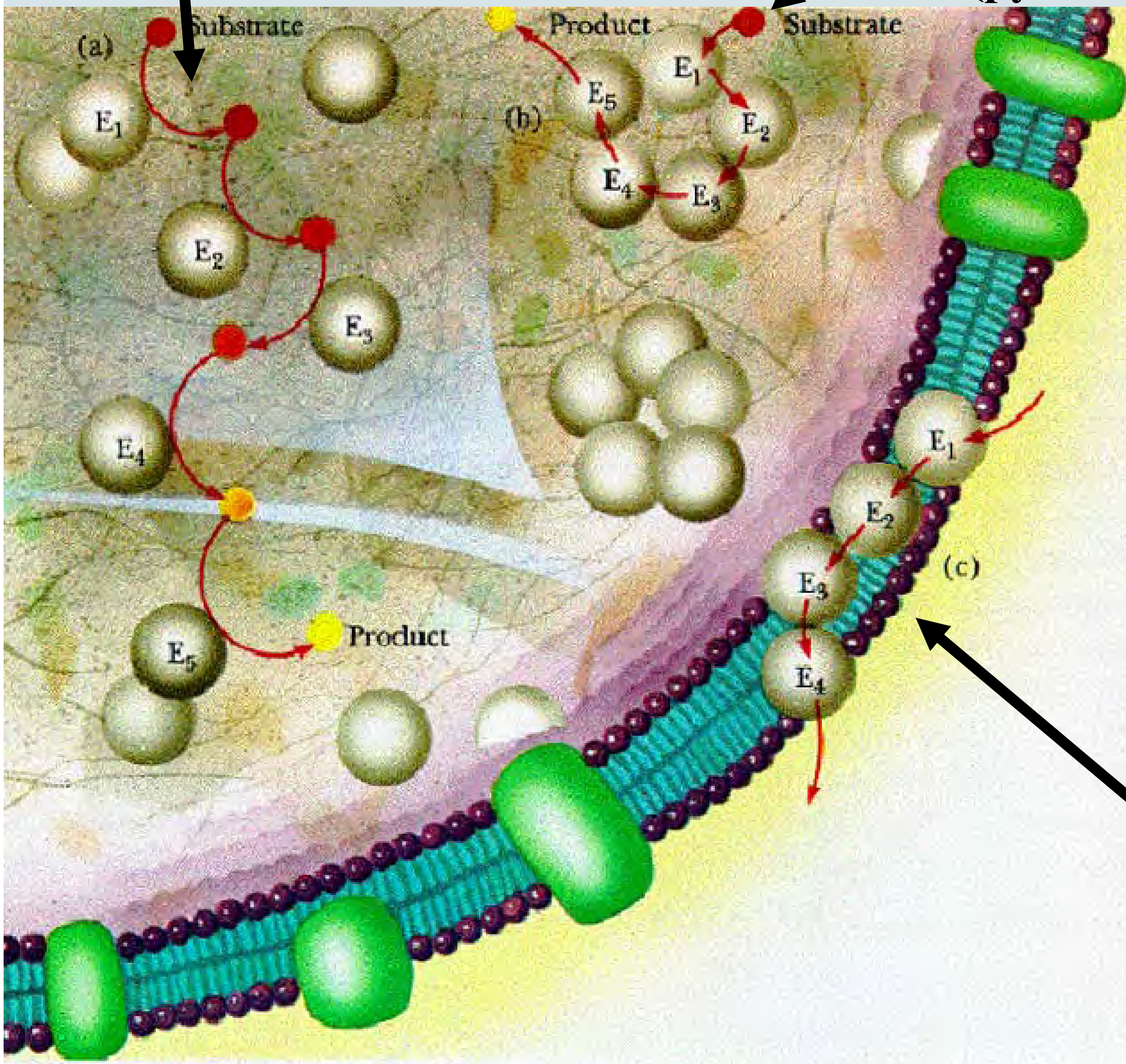


Nuclear membrane
Nucleolus
Nuclear pore
Nucleus
Ribosome
Cytosol
Cytoskeleton
Rough ER
Smooth ER
Golgi apparatus
Secretory vesicle
Centriole
Mitochondrion
Lysosome
Peroxisome
Plasma membrane

Separate enzymes with freely diffusing pathway intermediates (glycolysis)

Cytosolic multienzyme complex with intermediates channelled between enzymes (pyruvate dehydrogenase complex)



Membrane bound multienzyme complex (electron transport system)

Summary

1. The application of metabolic transformations is strongly organized.

2. This is a premise for development of metabolic simulators as a hierarchically organized list of reactions

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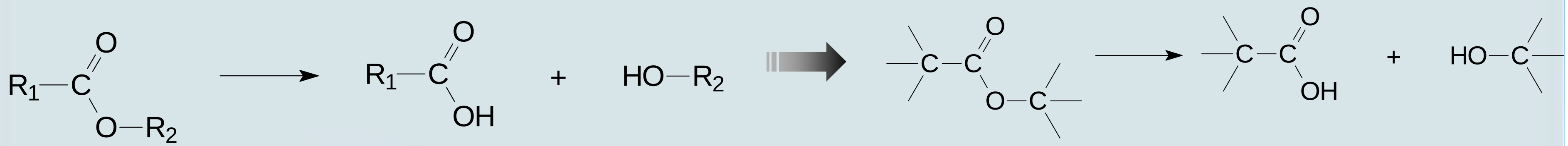
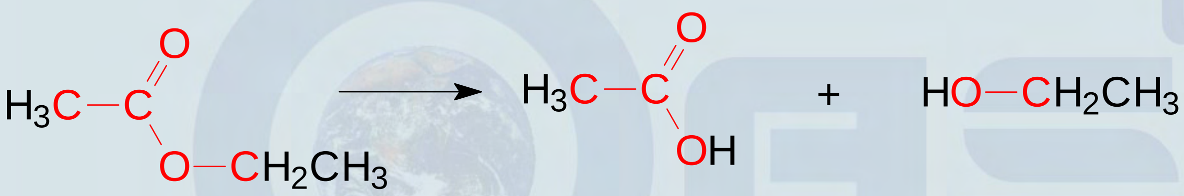
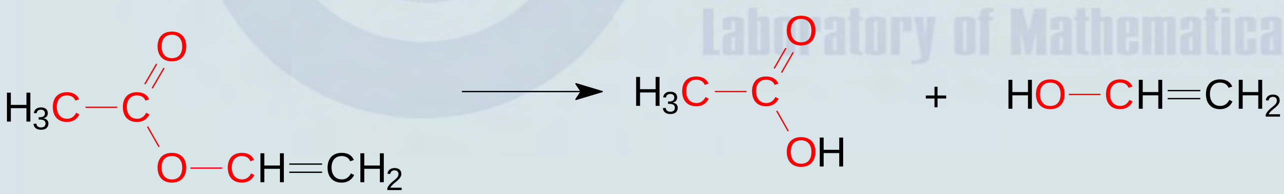
Simulation of molecular transformations



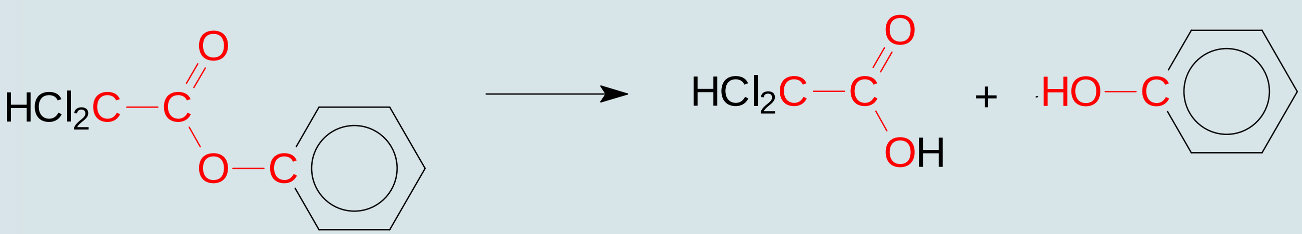
Half-lives,
25^0C, pH =7



2 years

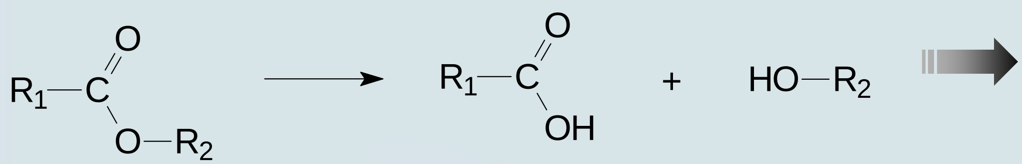


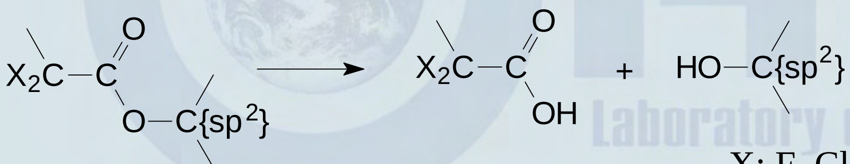
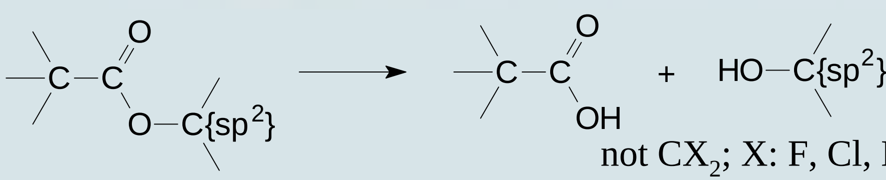
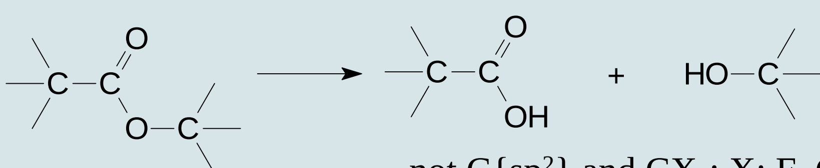
7 days



4 minutes

Simulation of molecular transformations



#	Transformation rules	Rate
1	 X: F, Cl, Br	High
2	 not CX_2; X: F, Cl, Br	Moderate
3	 not C{sp^2} and CX_2; X: F, Cl, Br	Low

Simulators of metabolism

Rule based systems

BESS **(P&G and Michigan State University)**
META **(MultiCASE Inc)**
METEOR **(Lhasa Ltd)**
CATABOL **(P&G and LMC, Bourgas As. Zlatarov University)**
TIMES **(LMC, Bourgas As. Zlatarov University)**
PPS **(UM-BBD, http://umbbd.msi.umn.edu/)**
MEPPS **(under development, Lhasa Ltd)**

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MEPPS (under development, Lhasa Ltd)

Simulators of metabolism

Rule based systems

METEOR **(Lhasa Ltd)**

PPS **(UM-BBD)**

- Very likely
- Likely
- Neutral
- Unlikely
- Very unlikely
- Unknown

Simulators of metabolism

Rule based systems

CATABOL **(P&G and LMC, Bourgas As. Zlatarov University)**
TIMES **(LMC, Bourgas As. Zlatarov University)**

$$\left\{\begin{matrix}\textbf{Probability}\\ \mathbf{k}\\ \mathbf{t_{1/2}}\end{matrix}\right\}$$

What is a *METABOLIC SIMULATOR?*

Prioritized list of molecular transformations and substructure matching engine applying it:

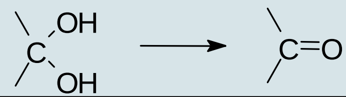
- **Including spontaneous and enzymatic reactions**
- **Probabilistic scheme for prioritization of reactions**
- **Organ / tissue specific**

Illustrating Basic Principles of the Metabolic Simulators

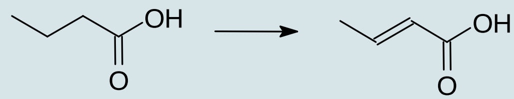
Simulator of metabolism

Principal transformations	Metabolites

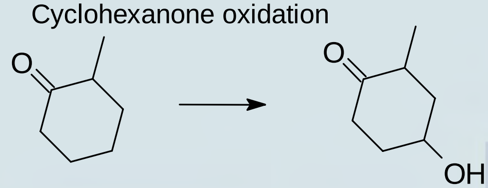
Geminal diol decomposition



β-oxidation

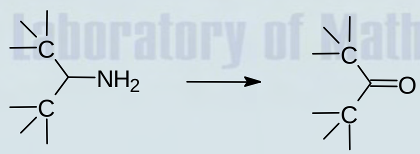


Cyclohexanone oxidation

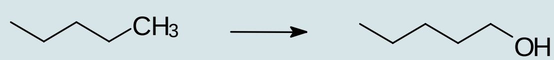


Ester hydrolysis

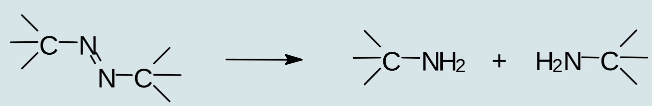
Amine decomposition



ω-Oxidation



Azo-bond cleavage



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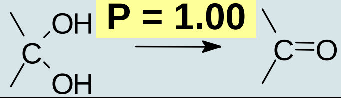
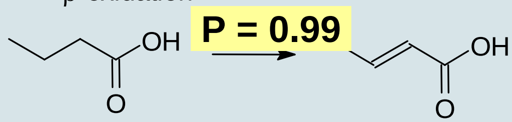
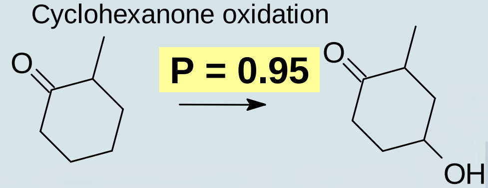
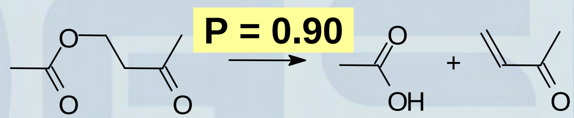
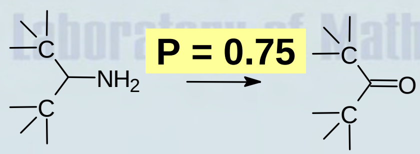
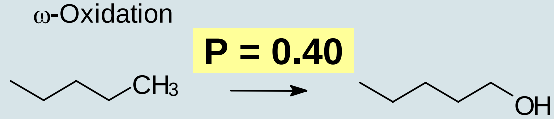
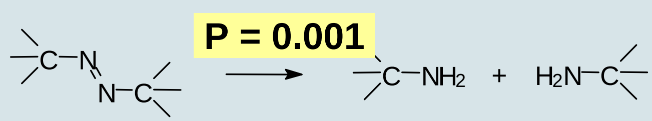
	Geminal diol decomposition 	
	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

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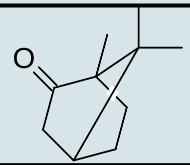
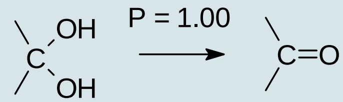
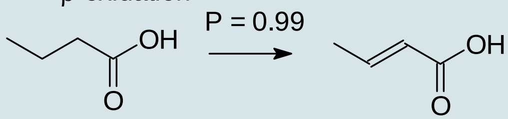
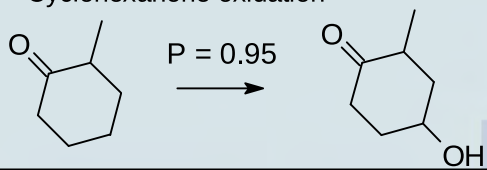
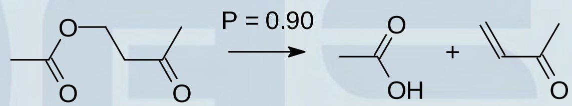
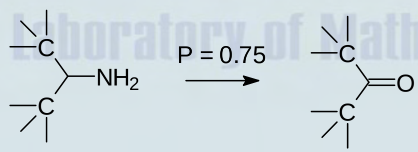
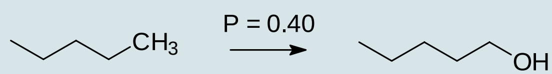
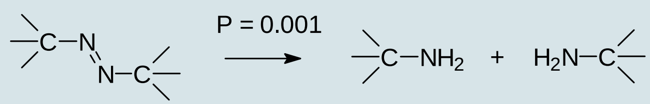
	Geminal diol decomposition 	
	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

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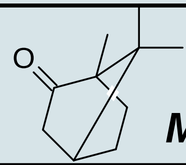
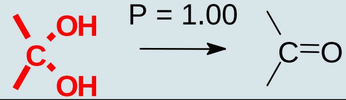
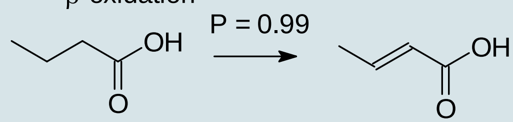
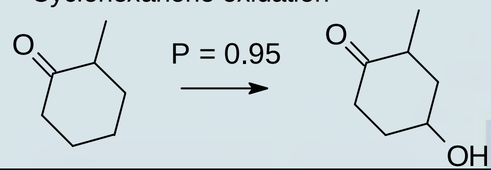
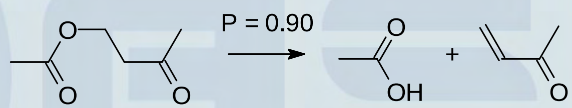
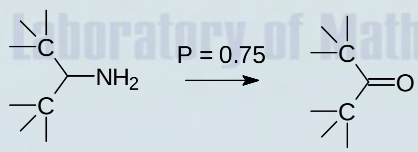
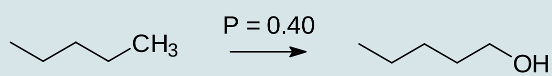
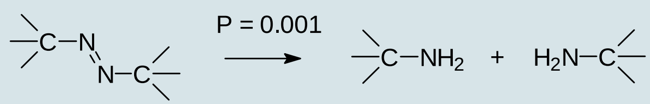
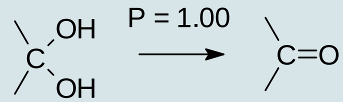
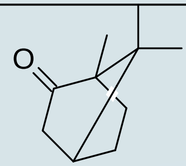
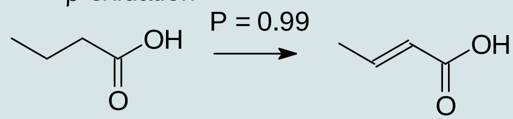
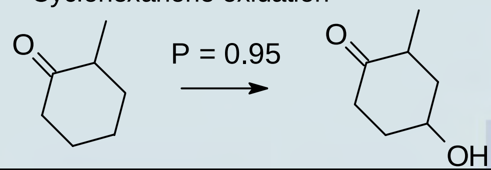
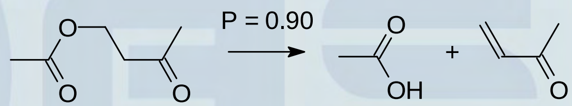
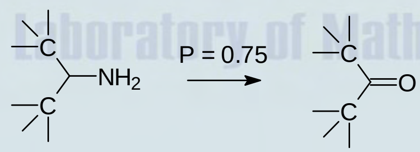
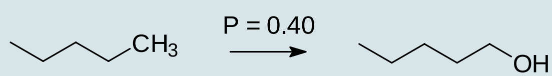
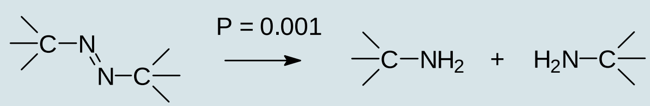
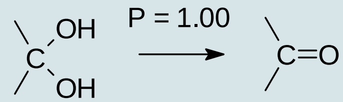
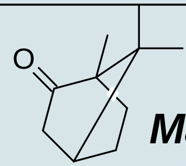
 ***Match? - No!***	Geminal diol decomposition 	
	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

Substrate	Principal transformations	Metabolites
	Geminal diol decomposition 	
	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

Substrate	Principal transformations	Metabolites

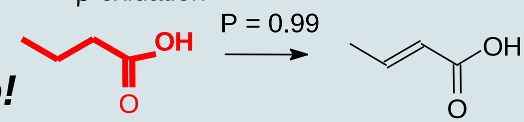
Geminal diol decomposition



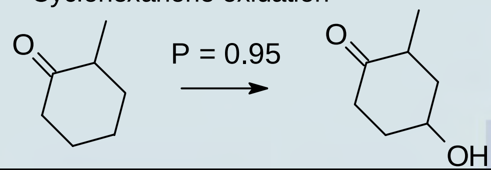


Match? - No!

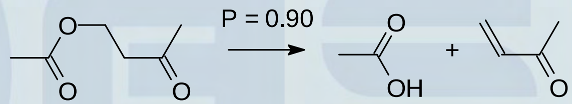
β-oxidation



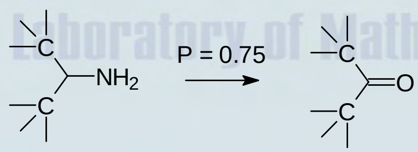
Cyclohexanone oxidation



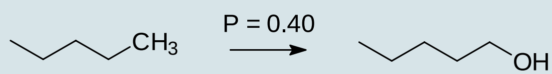
Ester hydrolysis



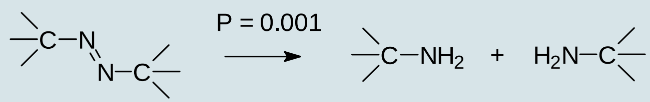
Amine decomposition



ω-Oxidation

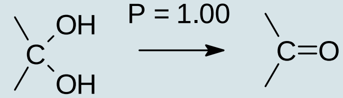


Azo-bond cleavage

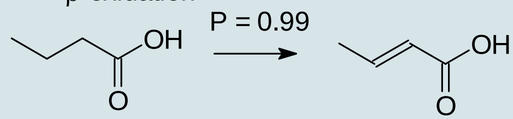


Substrate	Principal transformations	Metabolites

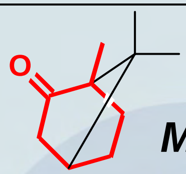
Geminal diol decomposition



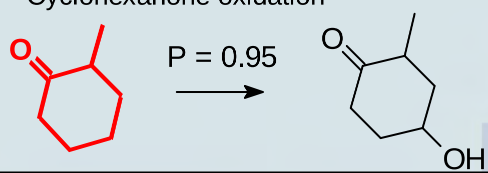
β-oxidation

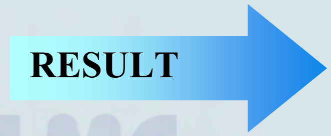


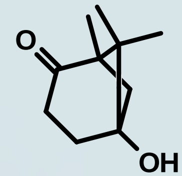
Cyclohexanone oxidation



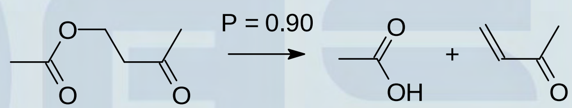
Match? - Yes!



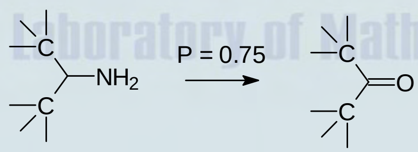




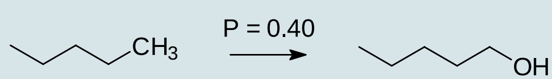
Ester hydrolysis



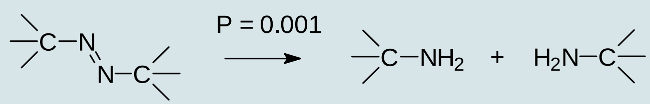
Amine decomposition

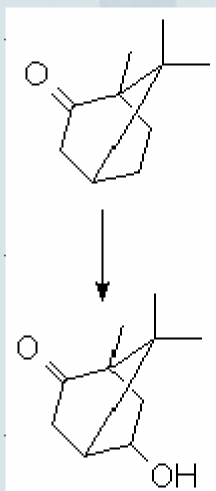


ω-Oxidation



Azo-bond cleavage

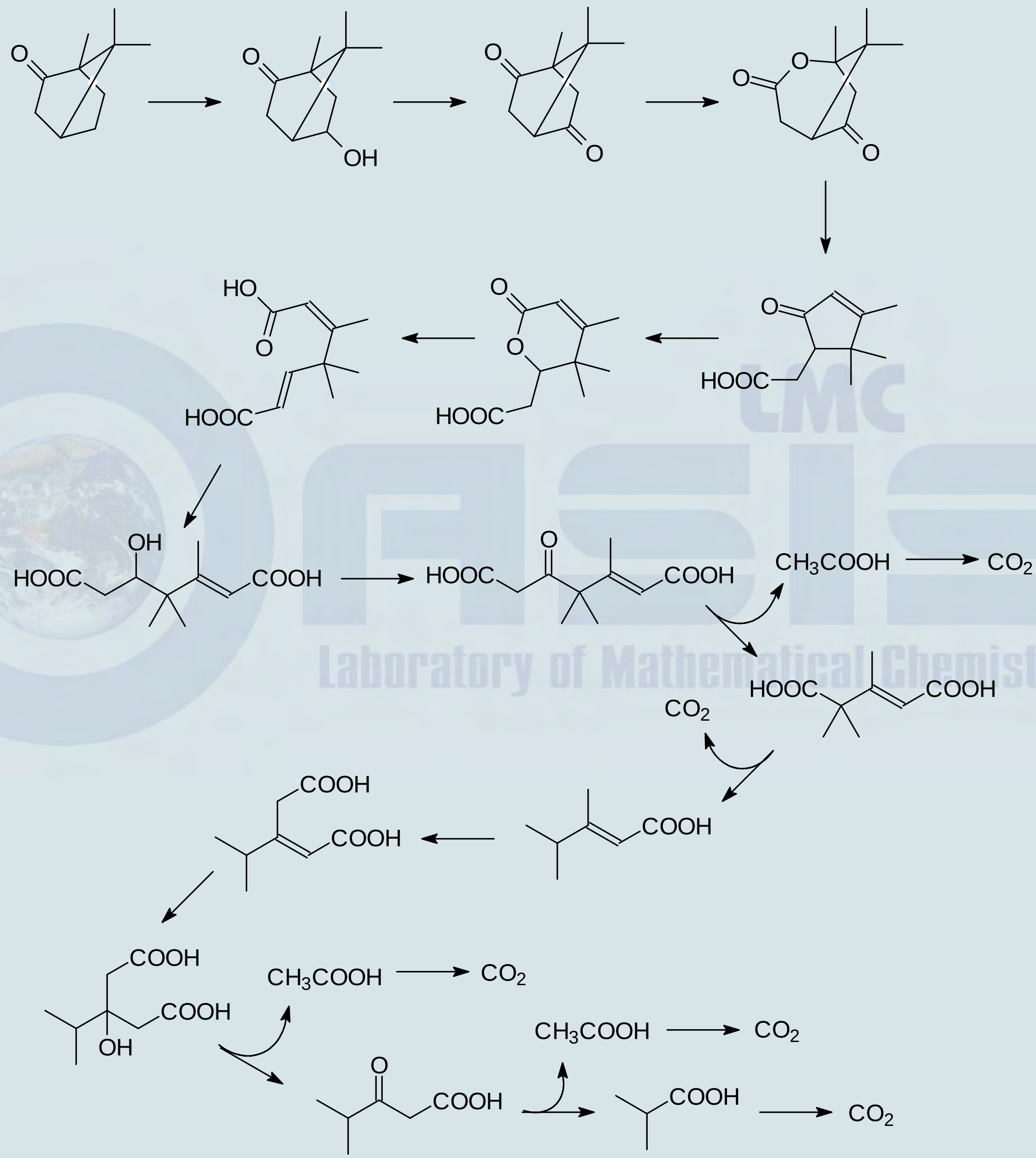


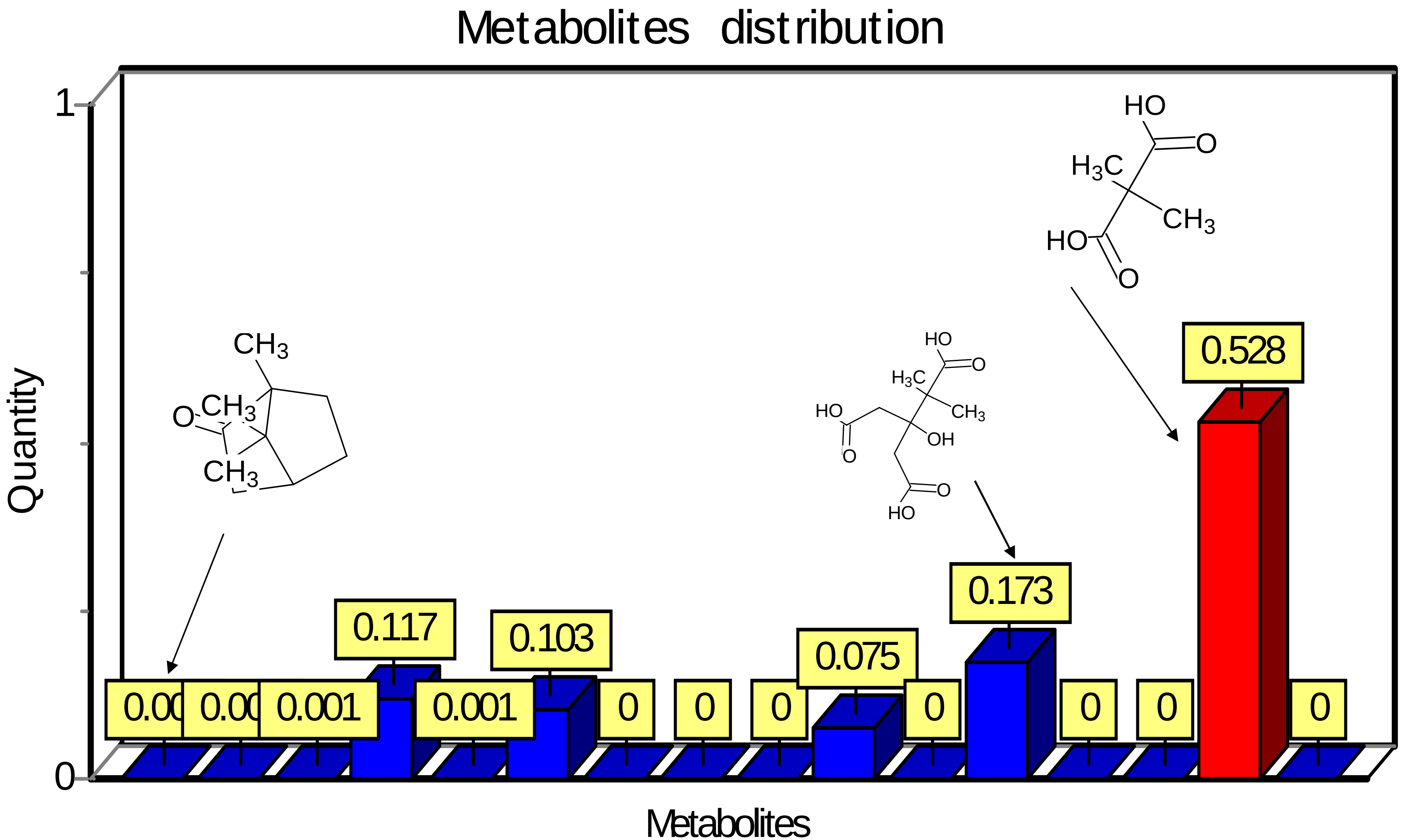


Outlook

- QSAR and Complexity of Chemical Structure
- Toxicity as a result of metabolic activation
- Metabolism logic
- Probabilistic approach to modeling metabolism
- CATABOL for simulating microbial degradation
- Performance and reliability of predicted metabolites
- Biodegradation kinetic models
- Simulating the effect of gene modification on metabolism

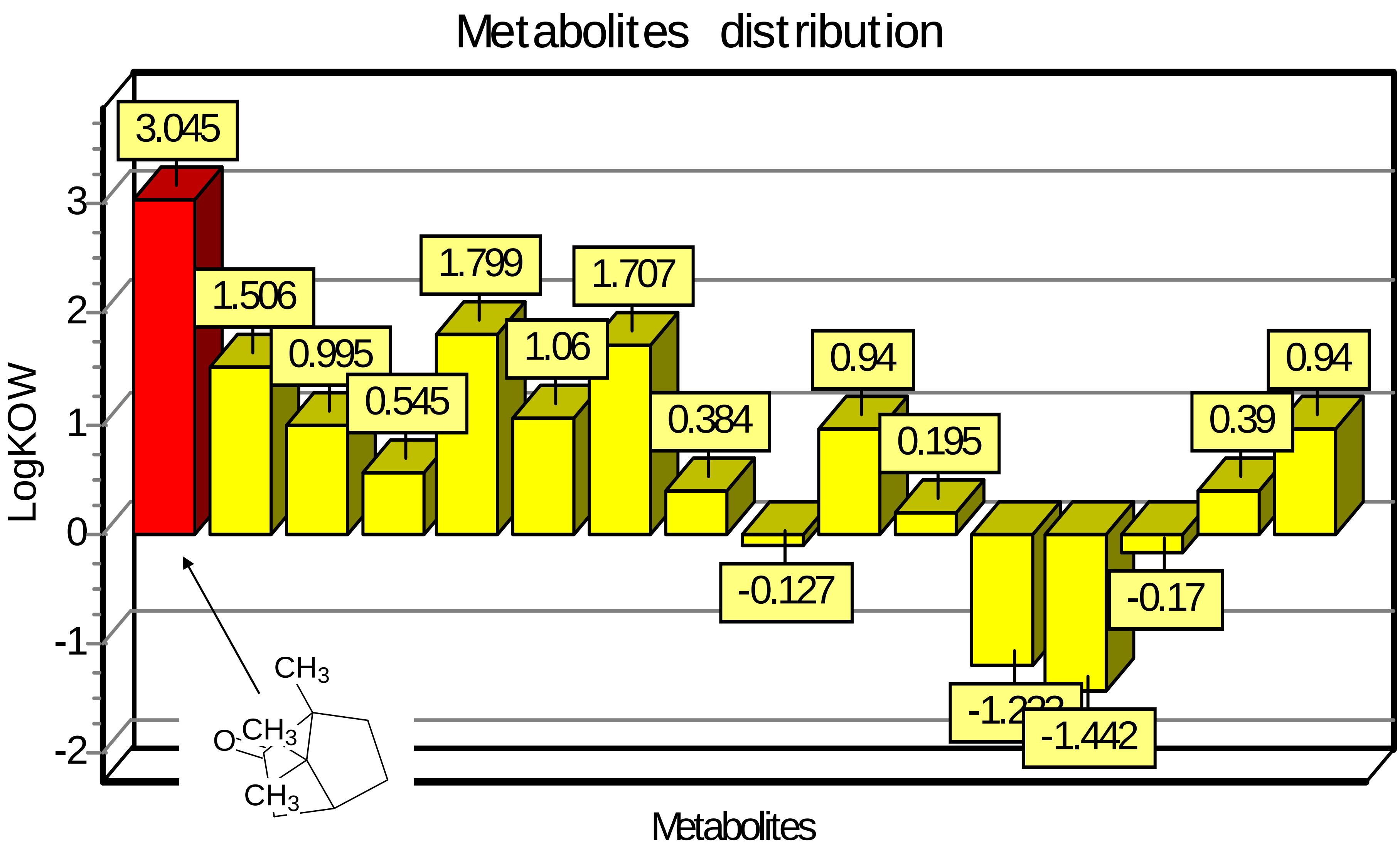
Predicted biotransformation pathway for camphor





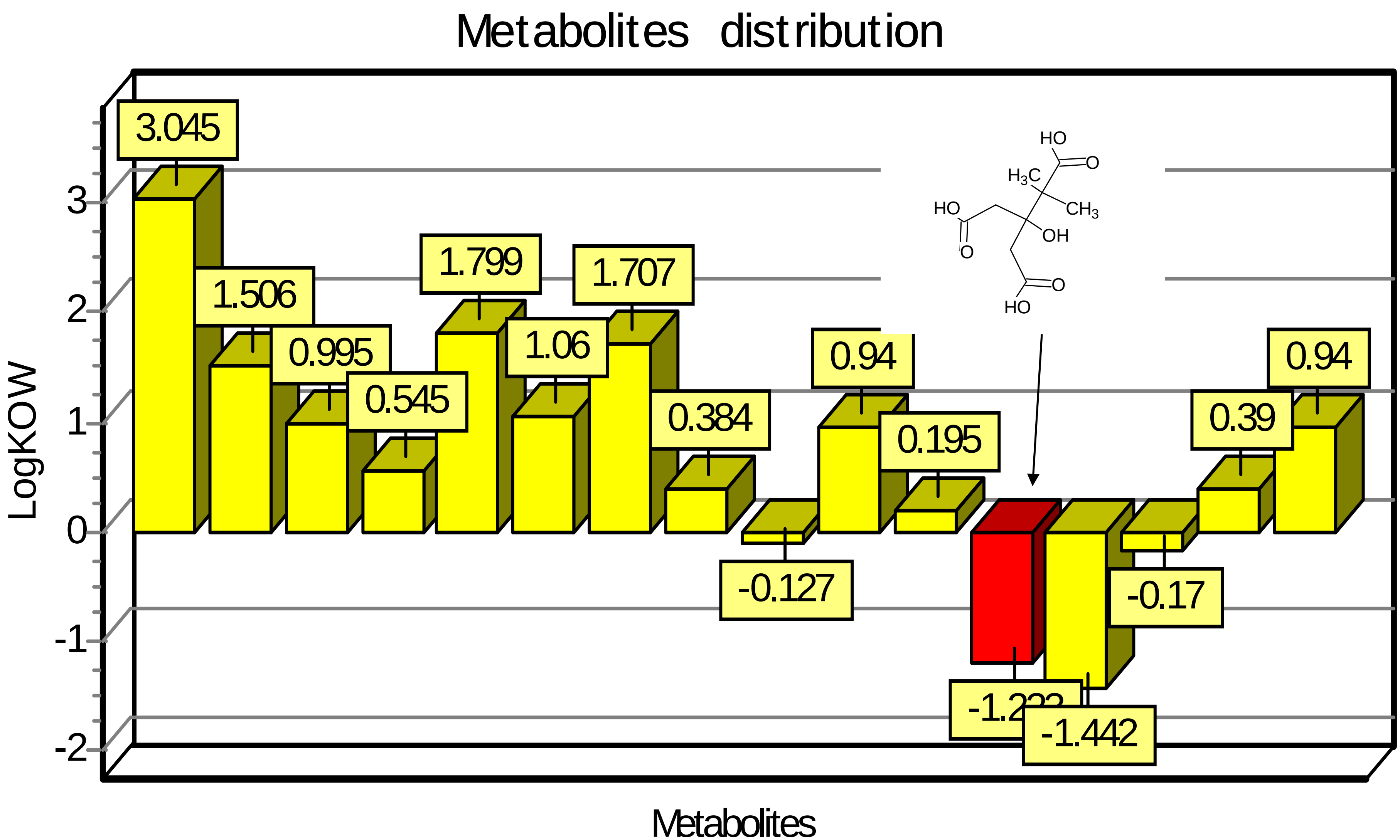
C(=O)(O)C(C)(C)C(=O)O; Q=0.528212; Po=0.529; Ps=0.528; logKOW=0.390

Transformation 394 Level 13



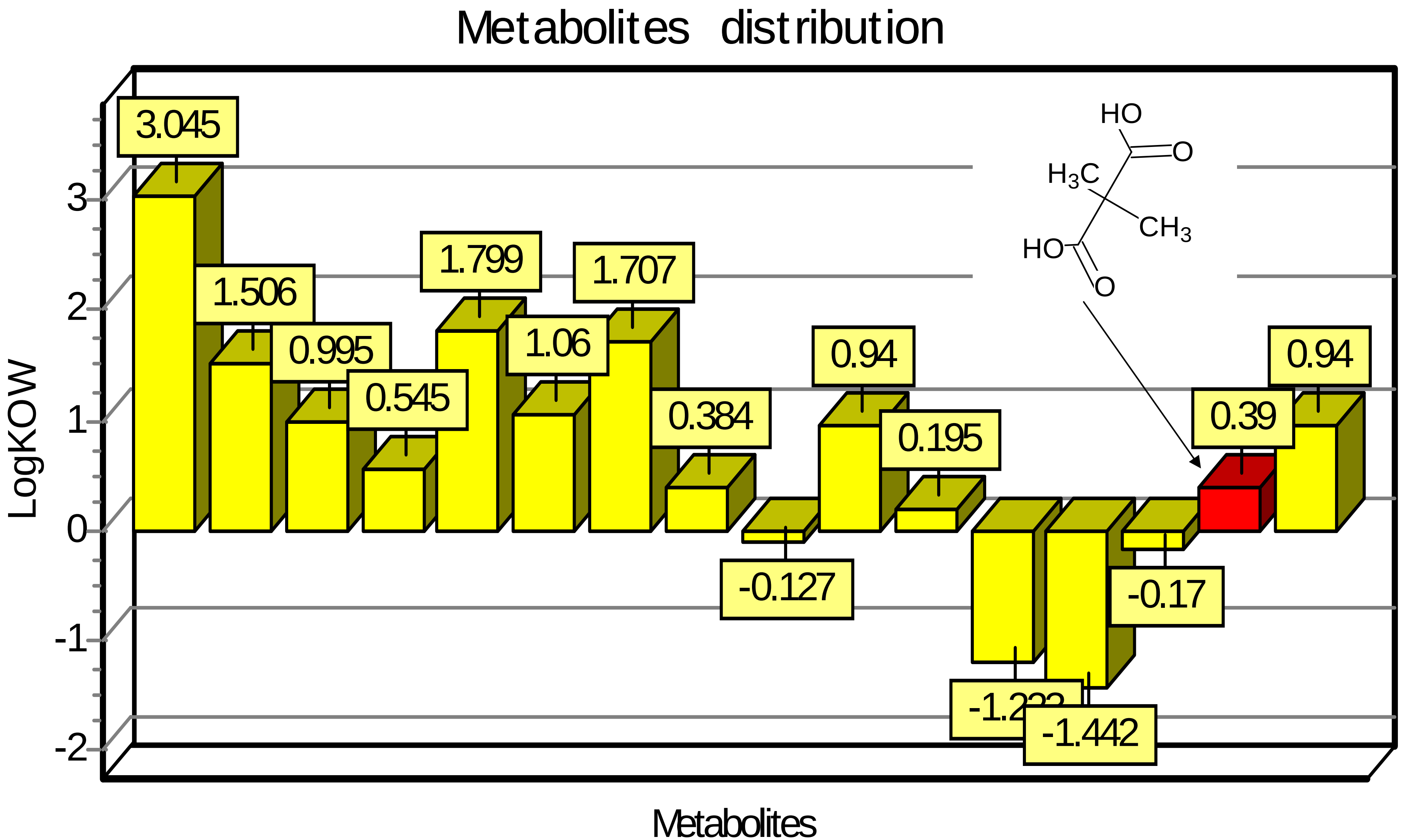
C1(=O)C2(C)C(C)(C)C(CC2)C1; Q=0.001000; Po=1.000; Ps=0.001; logKOW=3.045

Transformation 164 Level 0



C(=O)(O)C(C)(C)C(O)(CC(=O)O)CC(=O)O; Q=0.172507; Po=0.701; Ps=0.173; logKOW=-1.223

Transformation 281 Level 11



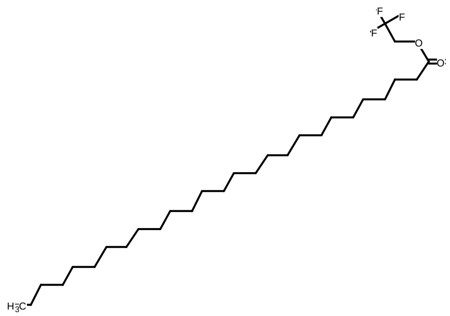
C(=O)(O)C(C)(C)C(=O)O; Q=0.528212; Po=0.529; Ps=0.528; logKOW=0.390

Transformation 394 Level 13

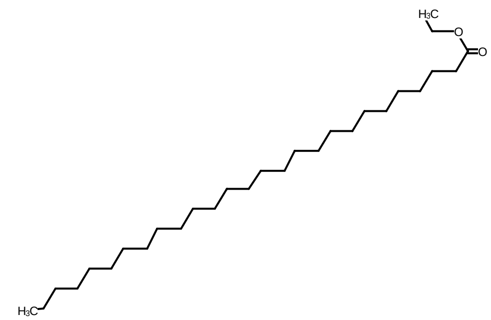
Persistency Evaluation Problems Solved by CATABOL

- **Chemicals with same BOD could have different fate**

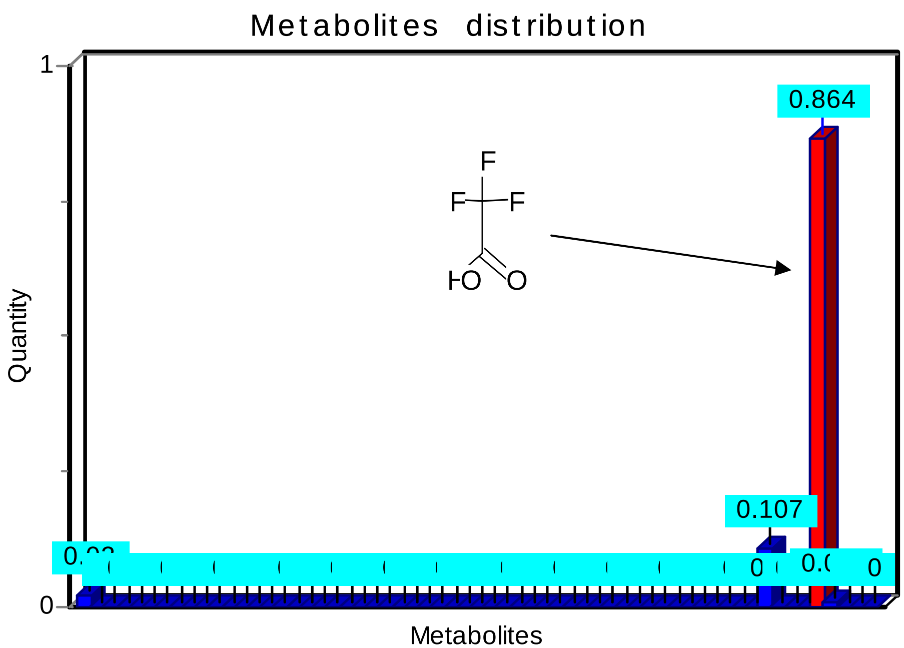
- **BOD is not indicative for obtaining stable degradants**



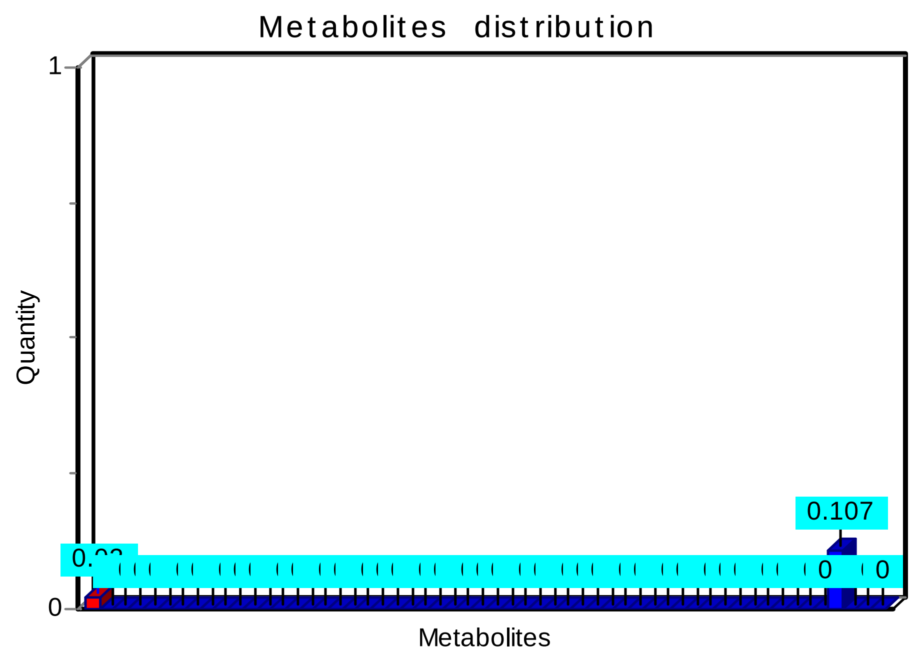
BOD = 95%



BOD = 97%



C(F)(F)(F)C(=O)O
Transformation 55, Quantity=0.8643



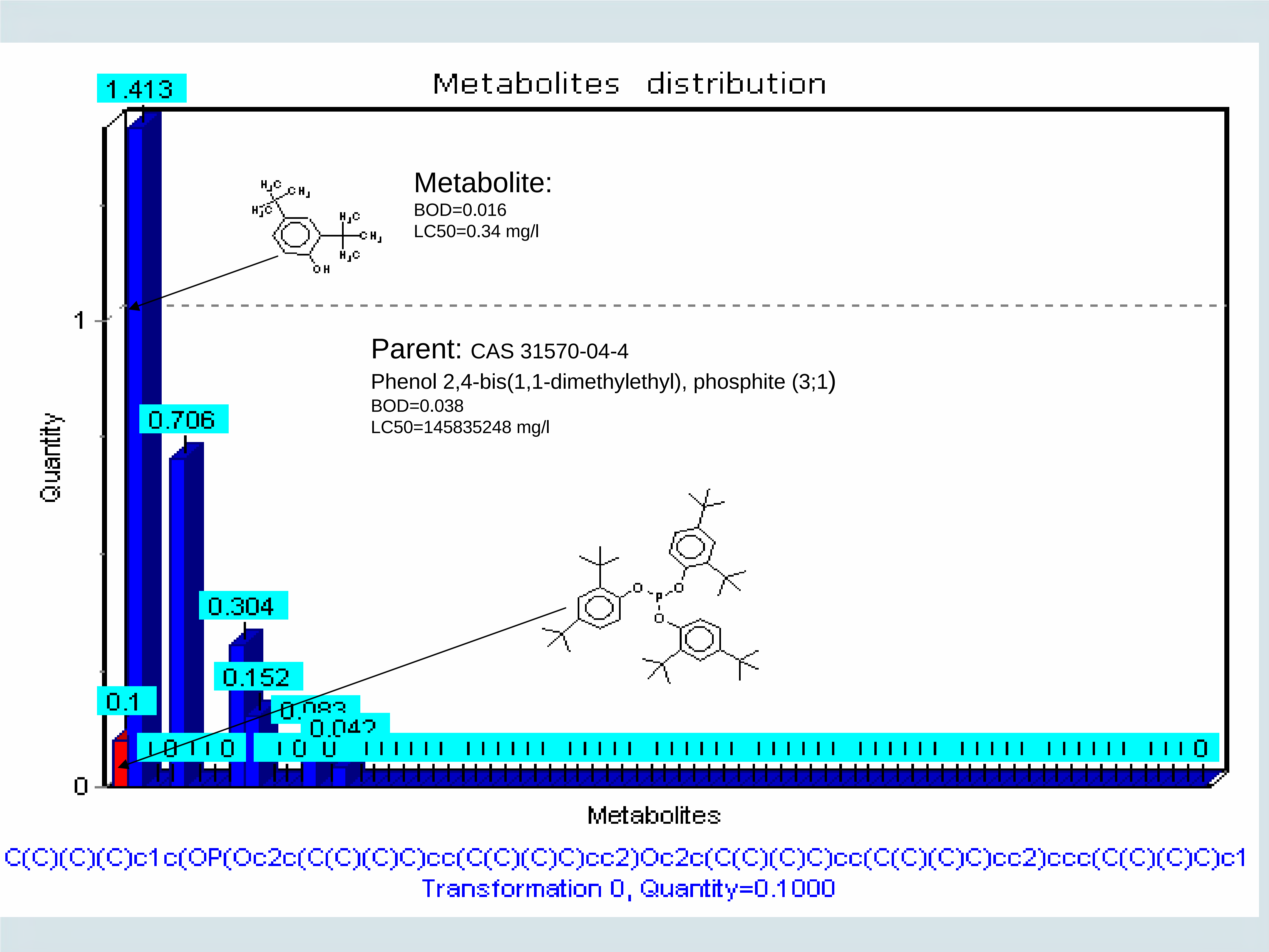
C(=O)(CCCCCCCCCCCCCCCCCCCCCCCCCC)OCC
Transformation 0, Quantity=0.0200

Persistency Evaluation Problems Solved by CATABOL

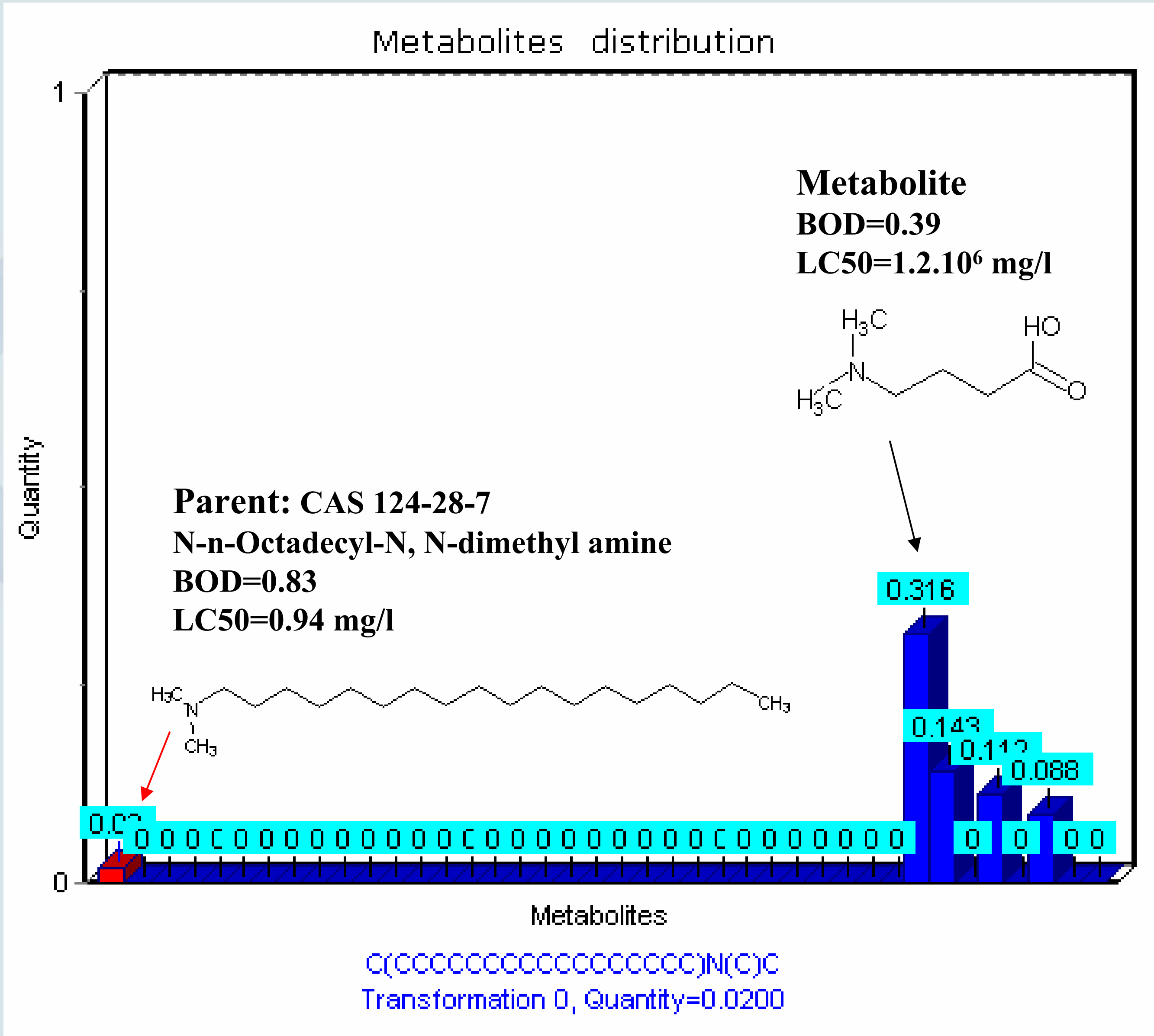
- **Chemicals with same BOD could have different fate**

- **BOD is not indicative for obtaining stable degradants**

- **Toxicity of chemicals could be due to the stable degradants**



Metabolites distribution
1.413
Metabolite:
BOD=0.016
LC50=0.34 mg/l
Parent: CAS 31570-04-4
Phenol 2,4-bis(1,1-dimethylethyl), phosphite (3;1)
BOD=0.038
LC50=145835248 mg/l
0.706
0.304
0.152
0.1
Quantity
Metabolites
1
0
C(C)(C)(C)c1c(OP(Oc2c(C(C)(C)C)cc(C(C)(C)C)cc2)Oc2c(C(C)(C)C)cc(C(C)(C)C)cc2)ccc(C(C)(C)C)c1
Transformation 0, Quantity=0.1000



Metabolites distribution
Quantity
1
0
Metabolite
BOD=0.39
LC50=1.2.10⁶ mg/l
H3C
HO
N
H3C
O
Parent: CAS 124-28-7
N-n-Octadecyl-N, N-dimethyl amine
BOD=0.83
LC50=0.94 mg/l
H3C
N
CH3
CH3
0.316
0.088
Metabolites
C(CCCCCCCCCCCCCCCCC)N(C)C
Transformation 0, Quantity=0.0200

Stable degradants in chemical legislation

Japanese NITE

Chemical Substances Control Law (CSCL)

The Features of the BCF Data Set under CSCL

Relationship between Biodegradation Test and Bioconcentration Test

Biodegradaton Test			Decision	Next Test
Method	Test Result			
Biodegradation Test (OECD 301C)	1	Parent Residual > 40% and Metabolite Residual < 1%	Not Readily Biodegradable	Bioconcentraiotn for Parent
	2	Parent Residual ≥ 1% and Metabolite Residual ≥ 1%		Bioconcentraiotn for Parent and Metabolite(s) (≥1%)
	3	Parent Residual < 1% and Metabolite Residual ≥ 1%		Bioconcentraiotn for Metabolite(s) (≥1%)
	4	Parent Residual ≤ 40% and Metabolite Residual < 1%	Readily Biodegradable	Nothing (Reguration Free)

Bioconcentration Test

OECD305C: The test fish (carp) is exposed to two concentrations of the test chemical substance in water under flow-through conditions.
All tests are conducted by GLP laboratories and their test results are reviewed by the joint council.

The Features of the BCF Data Set under CSCL

Relationship between Biodegradation Test and Bioconcentration Test

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	4	Parent Residual ≤ 40% and Metabolite Residual < 1%	Readily Biodegradable	Nothing (Reguration Free)

Bioconcentration Test

OECD305C: The test fish (carp) is exposed to two concentrations of the test chemical substance in water under flow-through conditions.
All tests are conducted by GLP laboratories and their test results are reviewed by the joint council.

CATABOL - mathematical formalism

BOD or CO_2 production

Modeled — **Theoretical**

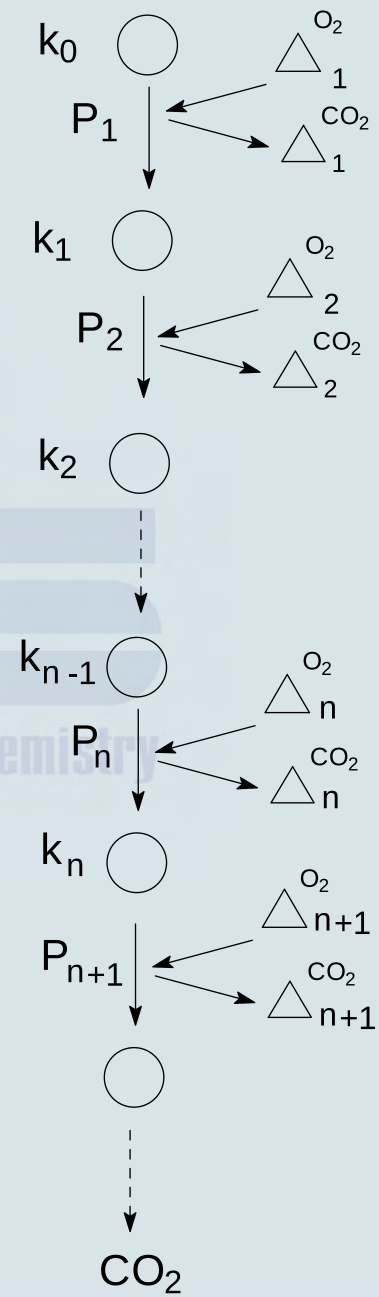
$$BOD = \sum_n \Delta_n^{O_2} \prod_{m=1}^{n} P_m \qquad BOD^{Th} = \sum_n \Delta_n^{O_2}$$

$$CO_2 = \sum_n \Delta_n^{CO_2} \prod_{m=1}^{n} P_m \qquad CO_2^{Th} = \sum_n \Delta_n^{CO_2}$$

Biodegradability - % of theoretical

$$BOD^{Calc} = \frac{\sum_n \Delta_n^{O_2} \prod_{m=1}^{n} P_m}{\sum_n \Delta_n^{O_2}} 100,\%$$

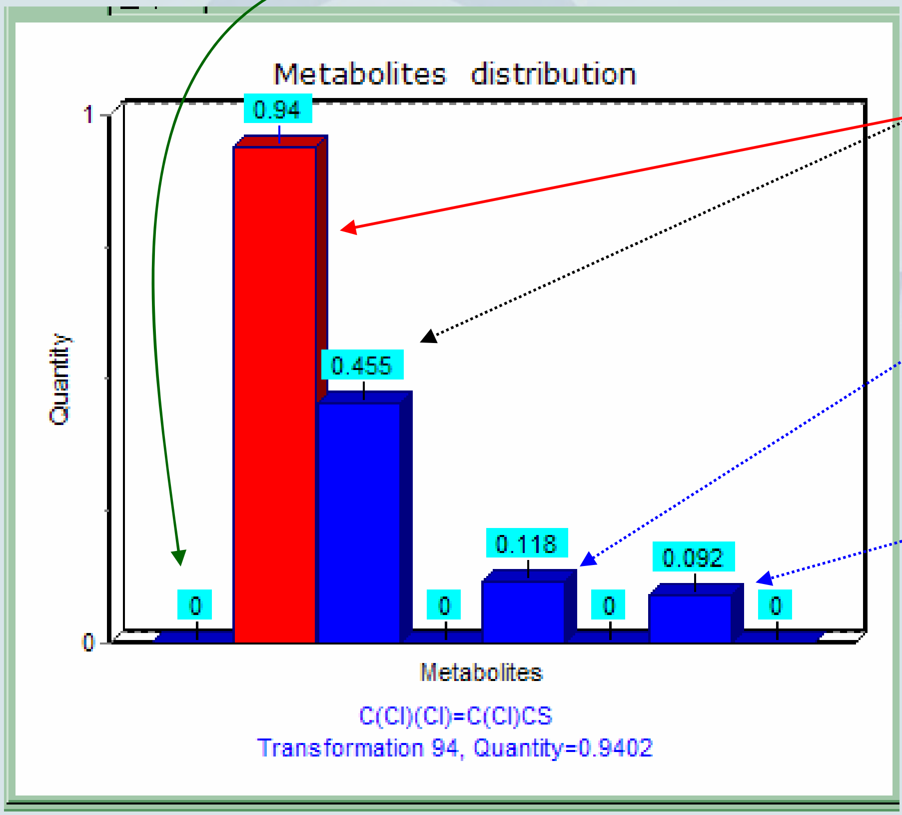
$$ThCO_2^{Calc} = \frac{\sum_n \Delta_n^{CO_2} \prod_{m=1}^{n} P_m}{\sum_n \Delta_n^{O_2}} 100,\%$$

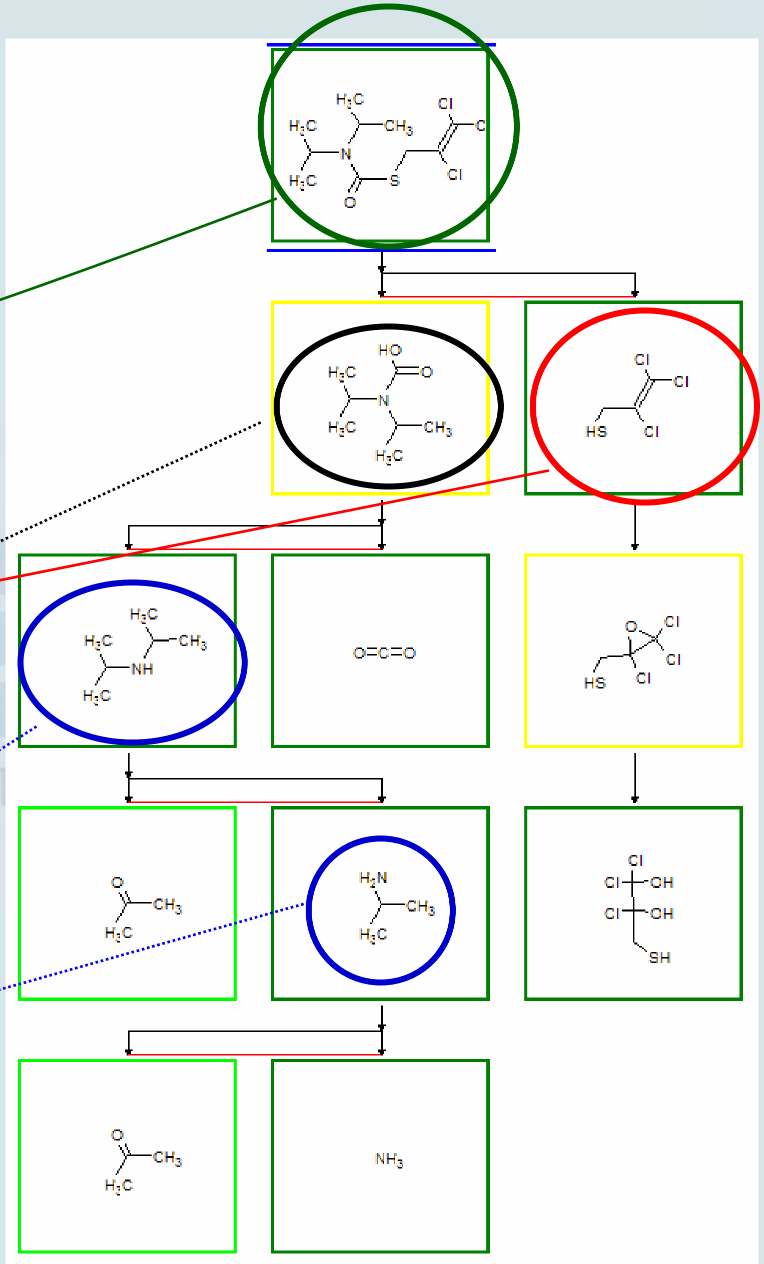


CATABOL - mathematical formalism

Quantities of metabolites

$$Q_n^{Calc} = \left(1 - P_{n+1}\right) \prod_{m=1 \to n} P_m, \text{ mol/mol parent}$$





CATABOL - mathematical formalism

First order kinetics

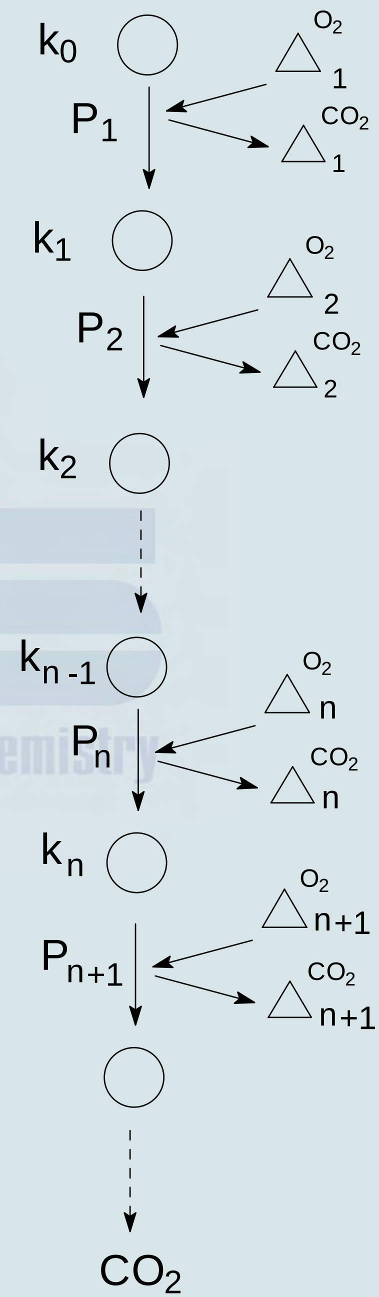
$$BOD = 100\left(1 - \exp\left(-kt\right)\right)$$

$$\mathrm{t}_{1/2} = \ln\left(2\right)/\mathrm{k}$$

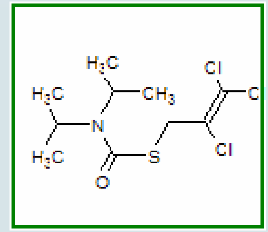
$$k = -\ln\left(1 - BOD_{28-d}^{Calc}/100\right)/\,28$$

Ultimate half-life

$$t_{1/2} = \frac{\ln\left(2\right)}{-\ln\left(1 - BOD_{28-d}^{Calc}/100\right)/\,28}$$



CATABOL - mathematical formalism



First order kinetics

$$BOD = 100\left(1-\exp(-kt)\right)$$

$$t_{1/2} = \ln(2)/k$$

$$k = -\ln\left(1 - BOD^{Calc}_{28-d}/100\right)/28$$

Ultimate half-life

$$t_{1/2} = \frac{\ln(2)}{-\ln\left(1 - BOD^{Calc}_{28-d}/100\right)/28}$$

$$BOD^{Calc} = 31\%$$

$$k = 0.013\,\text{day}^{-1}$$

$$t_{1/2} = 52\ \text{days}$$

CATABOL – training data

Observed BOD – Estimation of transformation probabilities

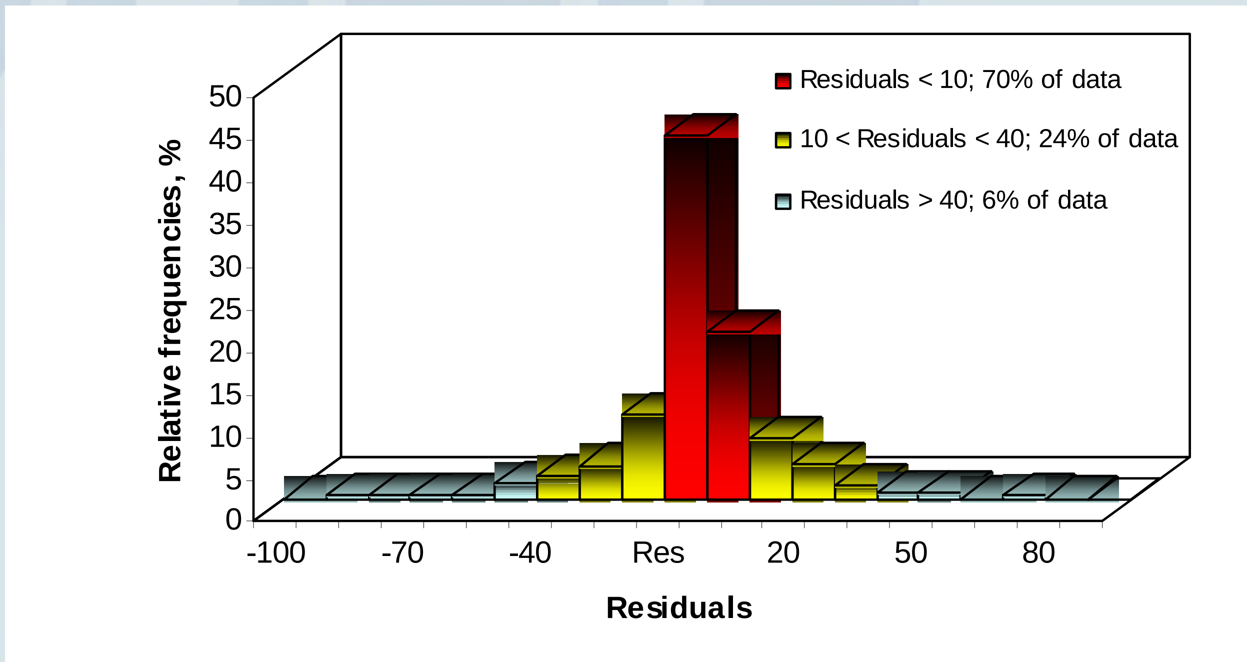
MITI I test (OECD 301 C)

745 training chemicals

347 external validation chemicals

$$\min_{P} RSS = \sum_{n=1}^{N}\left(BOD_n^{Obs.} - BOD_n^{Calc.}\right)^2$$

Coefficient of determination $R^2 = 0.69$
Sensitivity (ready biodegradable) - 86%
Specificity (not ready biodegradable) - 91%



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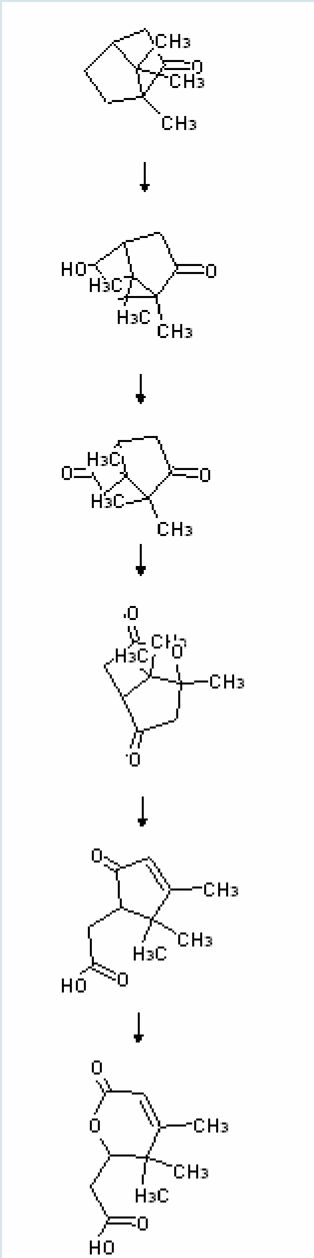
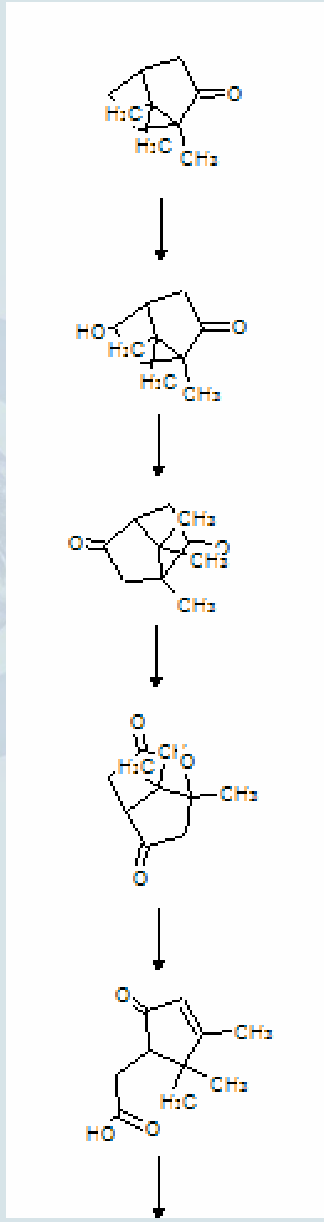
- Simulating the effect of gene modification on metabolism

How good is reproducibility of the observed catabolism?

Observed

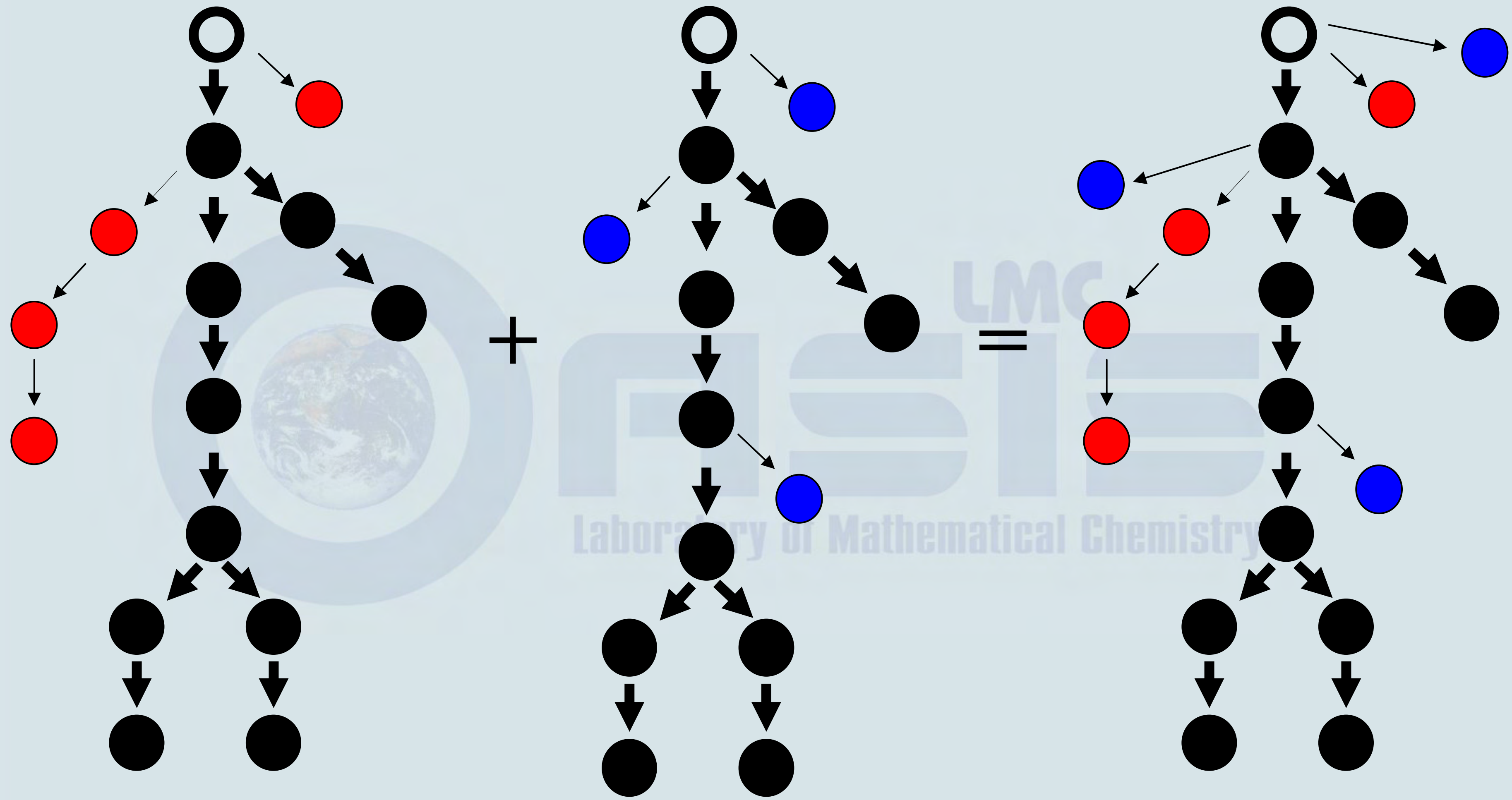


Predicted



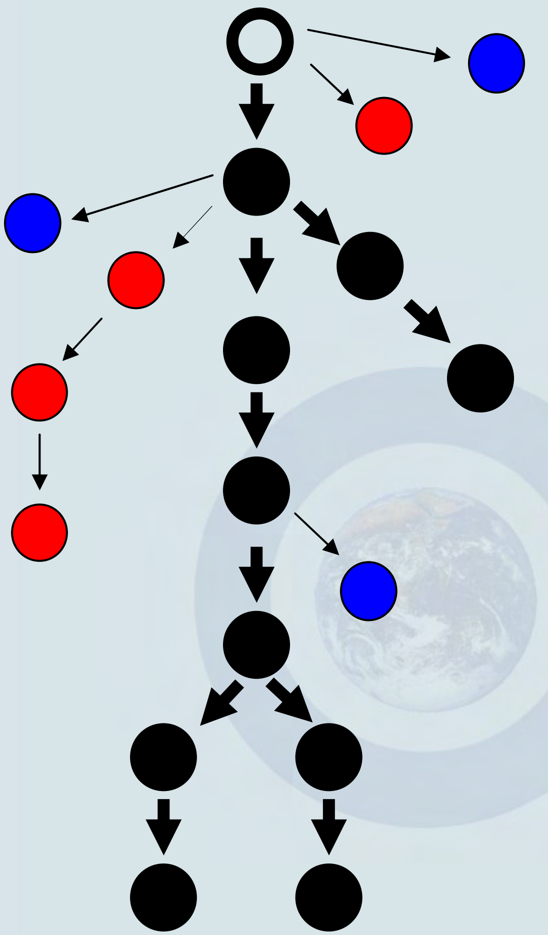
Observed versus simulated pathways

Observed and predicted catabolism **Union of pathways**



- Observed and predicted metabolites, $S_{\mathrm{Obs}} \cap S_{\mathrm{Pred}}$
- Observed and not predicted metabolites, $S_{\mathrm{Obs}} - S_{\mathrm{Pred}}$ or $S_{\mathrm{Obs}} \setminus S_{\mathrm{Pred}}$
- Predicted and not observed metabolites, $S_{\mathrm{Pred}} - S_{\mathrm{Obs}}$ or $S_{\mathrm{Pred}} \setminus S_{\mathrm{Obs}}$

Union of pathways



Probability that the metabolite is observed,
given that the metabolite is predicted (**predictability**)

$$\frac{Card\left(S_{\text{Obs}} \cap S_{\text{Pred}}\right)}{Card\left(S_{\text{Pred}}\right)} =$$

Probability that the metabolite is observed,
given that the metabolite is truly observed (**sensitivity**)

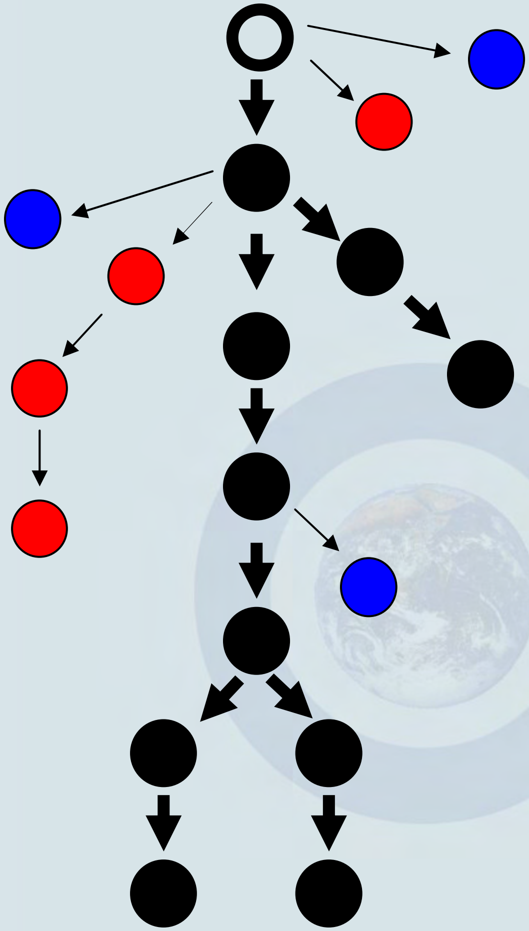
$$\frac{Card\left(S_{\text{Obs}} \cap S_{\text{Pred}}\right)}{Card\left(S_{\text{Obs}}\right)} =$$

- Observed and predicted metabolites, $S_{\text{Obs}} \cap S_{\text{Pred}}$

- Observed and not predicted metabolites, $S_{\text{Obs}} - S_{\text{Pred}}$ or $S_{\text{Obs}} \setminus S_{\text{Pred}}$

- Predicted and not observed metabolites, $S_{\text{Pred}} - S_{\text{Obs}}$ or $S_{\text{Pred}} \setminus S_{\text{Obs}}$

Union of pathways



Probability that the metabolite is not predicted given that the metabolite is truly observed (**false negatives**)

$$\frac{Card\left(S_{\text{Obs}} \setminus S_{\text{Pred}}\right)}{Card\left(S_{\text{Obs}}\right)} =$$

Probability that the metabolite is predicted given that the metabolite is truly not observed (**false positives**)

$$\frac{Card\left(S_{\text{Pred}} \setminus S_{\text{Obs}}\right)}{Card\left(S_{\text{Pred}}\right)} =$$

- Observed and predicted metabolites, $S_{\text{Obs}} \cap S_{\text{Pred}}$

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- Predicted and not observed metabolites, $S_{\text{Pred}} - S_{\text{Obs}}$ or $S_{\text{Pred}} \setminus S_{\text{Obs}}$

Reliability of generated metabolic pathway

$N_{i,succ}^{TR}$ **- the numbers of successful applications of the transformation**

$N_{i,fail}^{TR}$ **- the numbers of unsuccessful applications of the transformation**

Reliability of *i*-th transformation

$$R_i^{TR} = \frac{N_{i,succ}^{TR}}{N_{i,succ}^{TR} + N_{i,fail}^{TR}}$$

Reliability of predicted *l*-th metabolite

$$R_l^M = \prod_{j=1}^{J} R_j^{TR}$$

Reliability of *k*-th map

$$R_k^{Map} = \frac{\sum_{j=1}^{K} R_k^M}{K}$$

CATABOL – Applicability domain

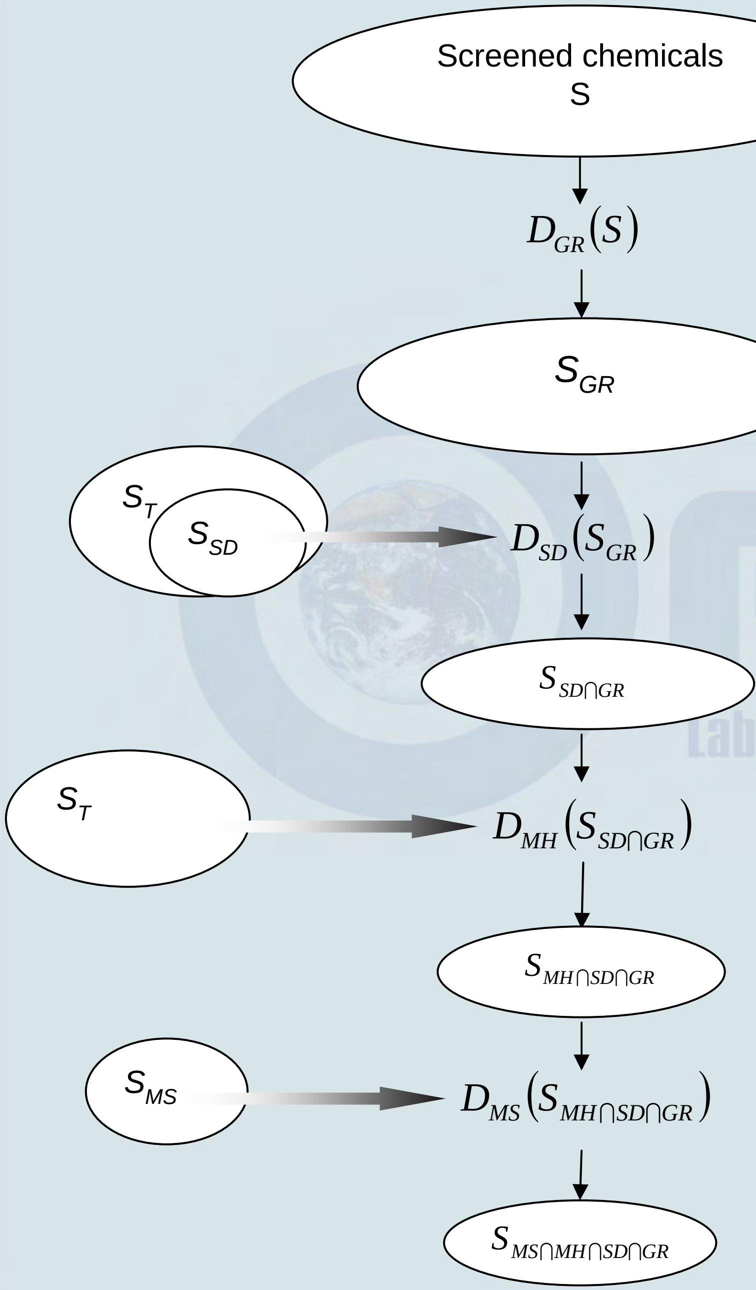
Model: **Bird or Fish?**

Applicability domain

Discrimination of predictions

Training data
External validation data
Modeled hypothesis
Statistics
Application of the model

CATABOL – Applicability domain



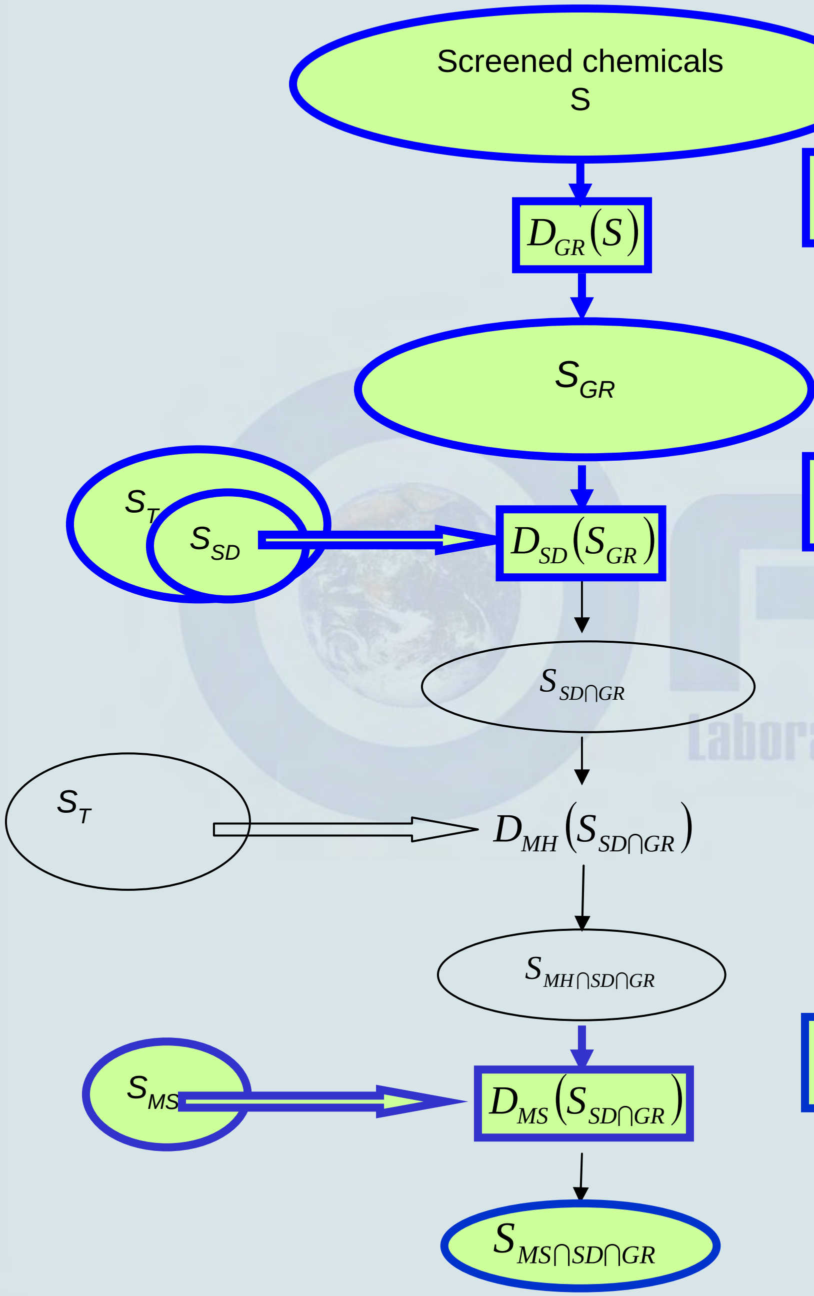
I. General requirements

II. Structural domain

III. Mechanistic domain

IV. Metabolic simulator domain

CATABOL – Applicability domain



I. General requirements

Molecular weight, *MW* ϵ 44 ÷ 960

II. Structural domain

Atom-centered fragments accounting for:

Attached H atoms

First neighbors (Csp^3 or Car) atom

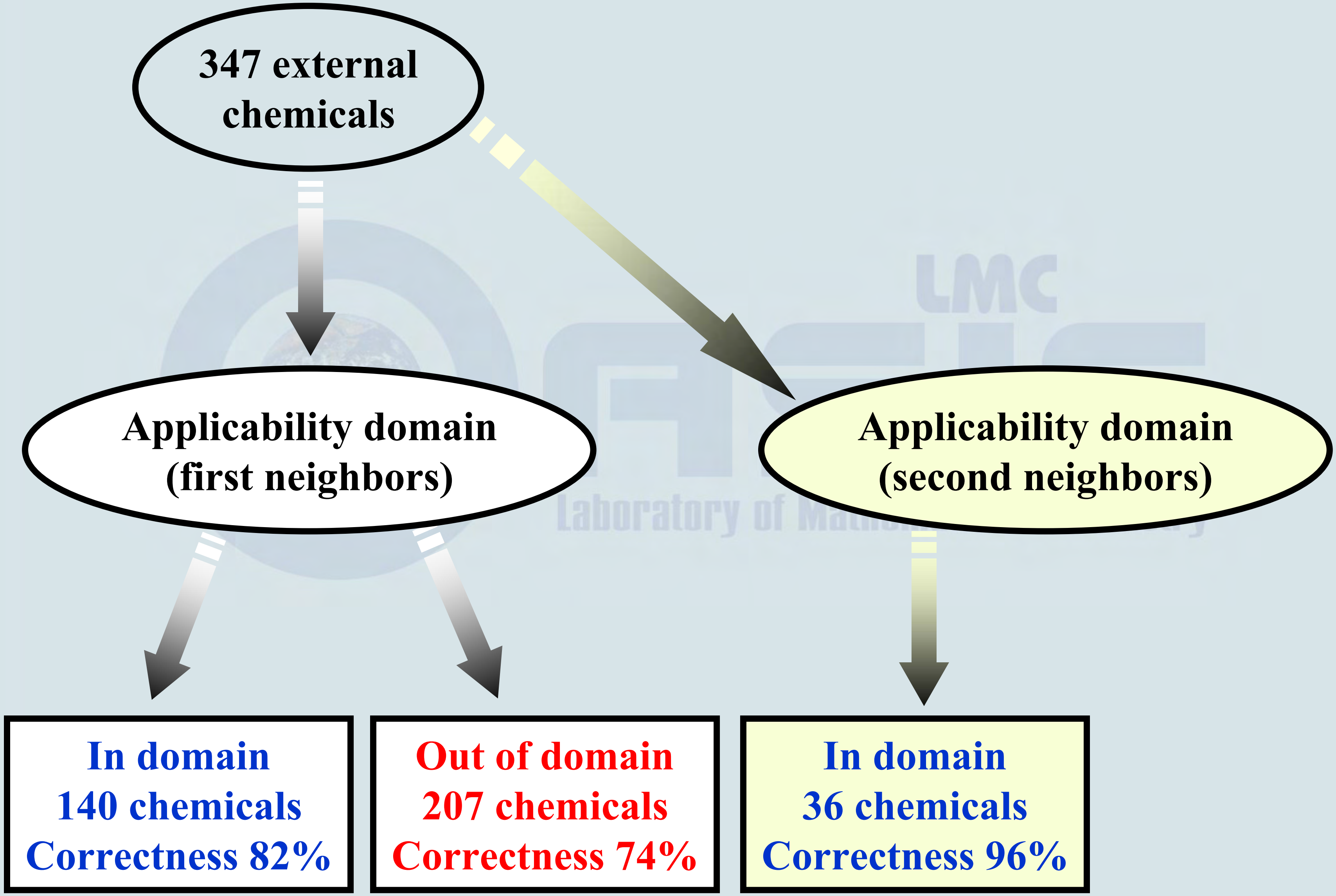
10 bonded non (Csp^3 or Car) atom are considered as a single neighbor

IV. Metabolic simulator domain

Unable to simulate catabolism:

Due to lack of suitable transformation

CATABOL – Applicability domain



External Validation of CATABOL based on OECD principle

National Institute of Technology and Evaluation (NITE)
Japan, 2005

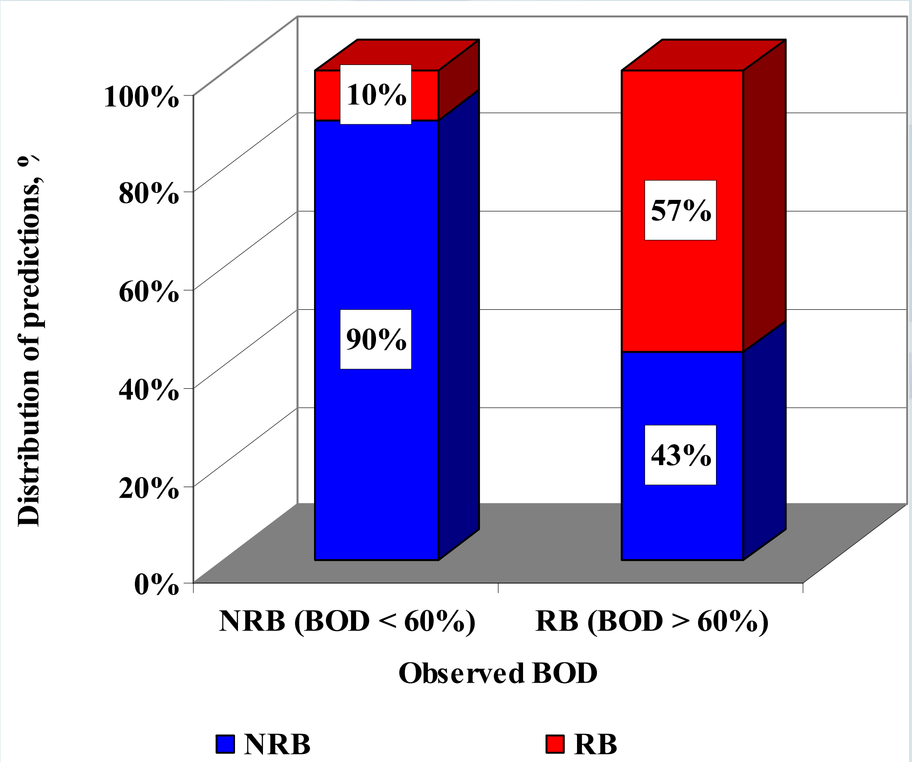
Used data for external validation

Test: OECD 301 C (MITI I)

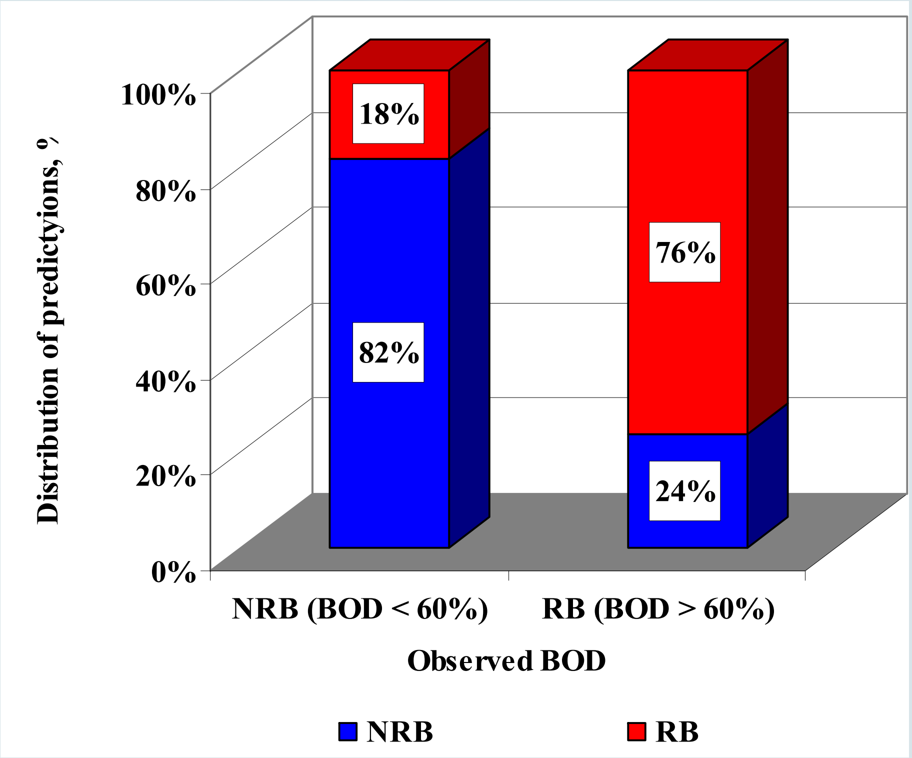
Existing chemical:	**338**
New chemicals:	**1123**
Total:	**1461**

Statistics

Without accounting for domain



Accounting for domain



Summary

The committee recommended that……

- Four biodegradation models (BIOWIN5,6 CERI model CATABOL) are acceptable for using for the screening purpose.
- CATABOL should be used mainly because CATABOL is only model that is based on biodegradation pathway and provide many useful information to assess the biodegradability of a chemicals.
- In addition, CERI model and BIOWIN5 should be used to obtain prediction from different view point.

Summary
NITE

The committee recommended that……

- Four biodegradation models (BIOWIN5,6 CERI model CATABOL) are acceptable for using for the screening purpose.
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Outlook

- QSAR and Complexity of Chemical Structure
- Toxicity as a result of metabolic activation
- Metabolism logic
- Probabilistic approach to modeling metabolism
- CATABOL for simulating microbial degradation
- Performance and reliability of predicted metabolites
- Biodegradation kinetic models
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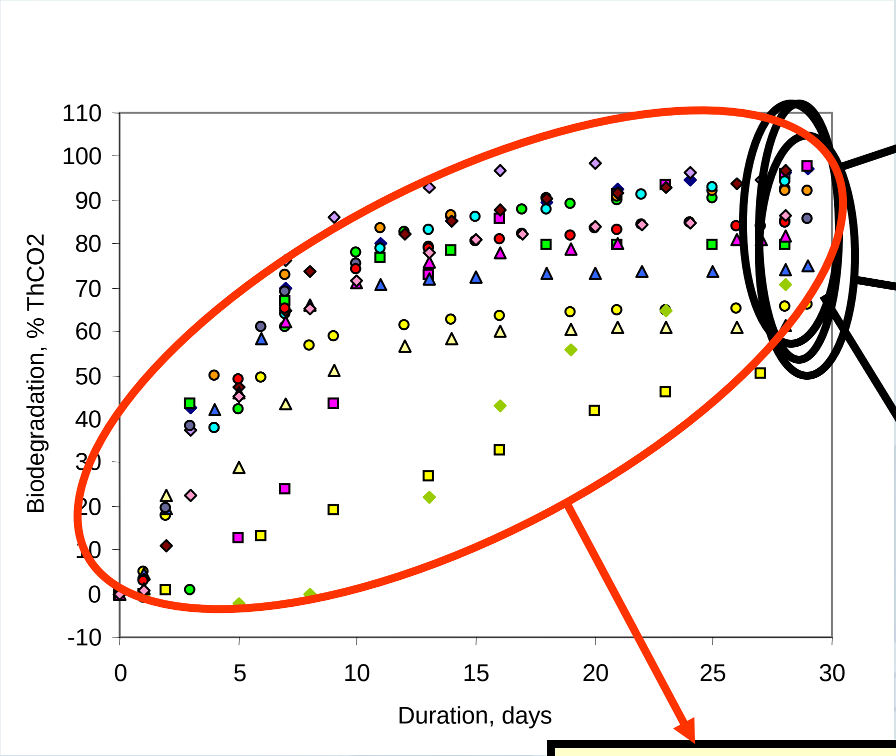
Kinetic Models

Cooperation with BASF, ExxonMobil, Givaudan, Dow Chemicals

CATABOL^TD – time dependent model



MITI I test: 1090 chemicals
%ThOD at 28th day

MITI I test: 266 chemicals
Metabolites quantities at 28th day

OECD 301B: 108 chemicals
$\%ThCO_2$ at 28th day

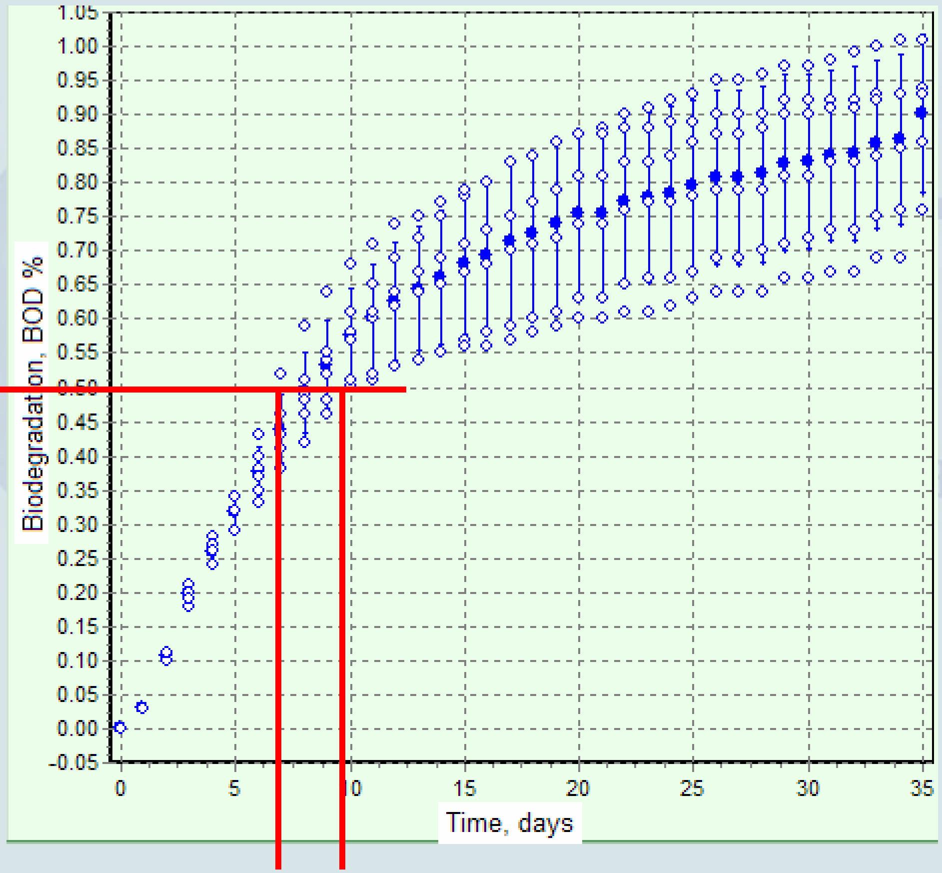
BASF: 301A-F, ISO 14593: ~ 500 chemicals
Time series for %DOC, %ThOD or $\%ThCO_2$

Metabolic studies with microorganisms: ~ 300 chemicals
(*Pseudomonas*, *Sphingomonas*, *Rhodococcus*, etc.)
Documented metabolic pathways

CATABOL^{TD} – time dependent model

Training data

BOD = 50%



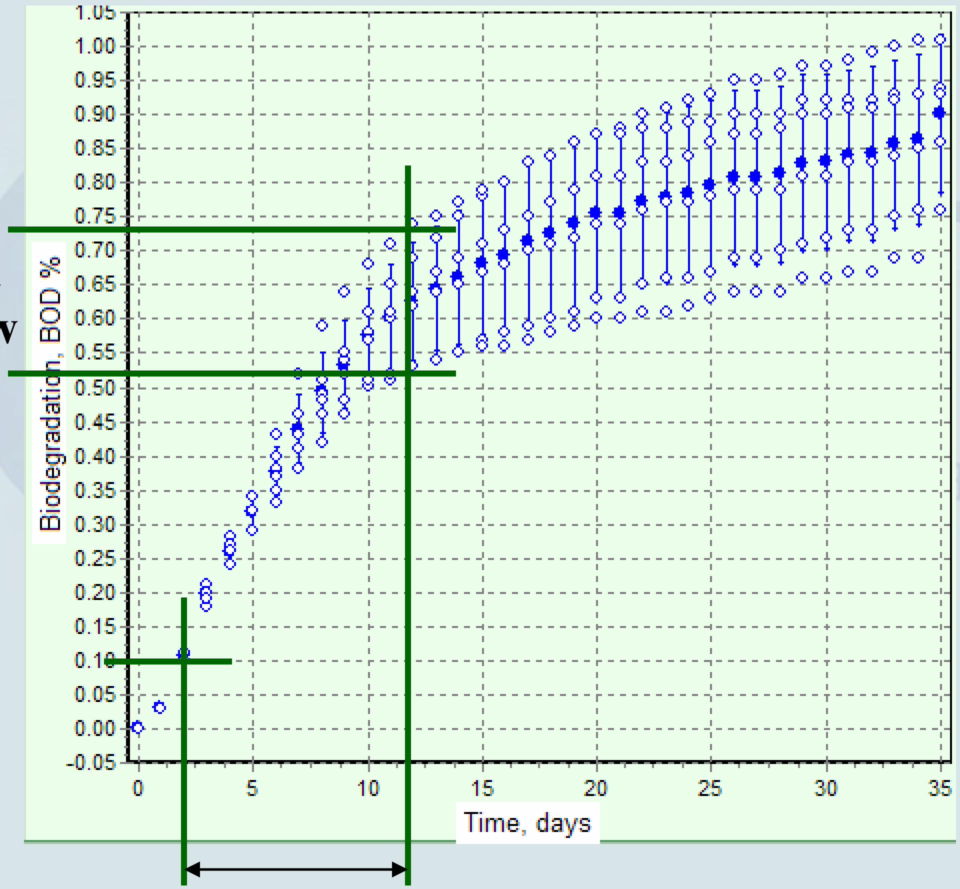
$t_{1/2}^{\text{Ultimate}}$

Ultimate half life

CATABOL^TD – time dependent model

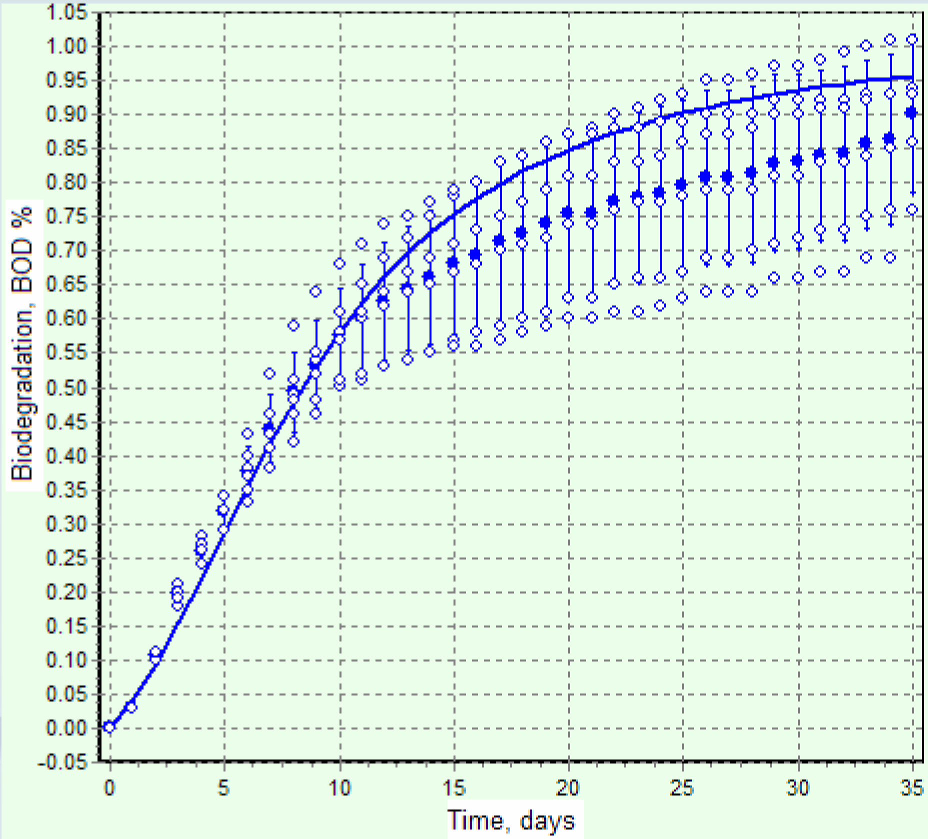
Training data

BOD within
10-d window



10-d window

CATABOL^{TD} – time dependent model



$$BOD^{Calc} = f\left(P_i\right) = f\left[P_i\left(k_i, t\right)\right]$$

$$\min_{\mathbf{k}} RSS = \sum_{\mathrm{n}} \sum_{t} \left(BOD_{n,t}^{Obs} - BOD_{n,t}^{Calc}\right)^2$$

P approximated by first order kinetics

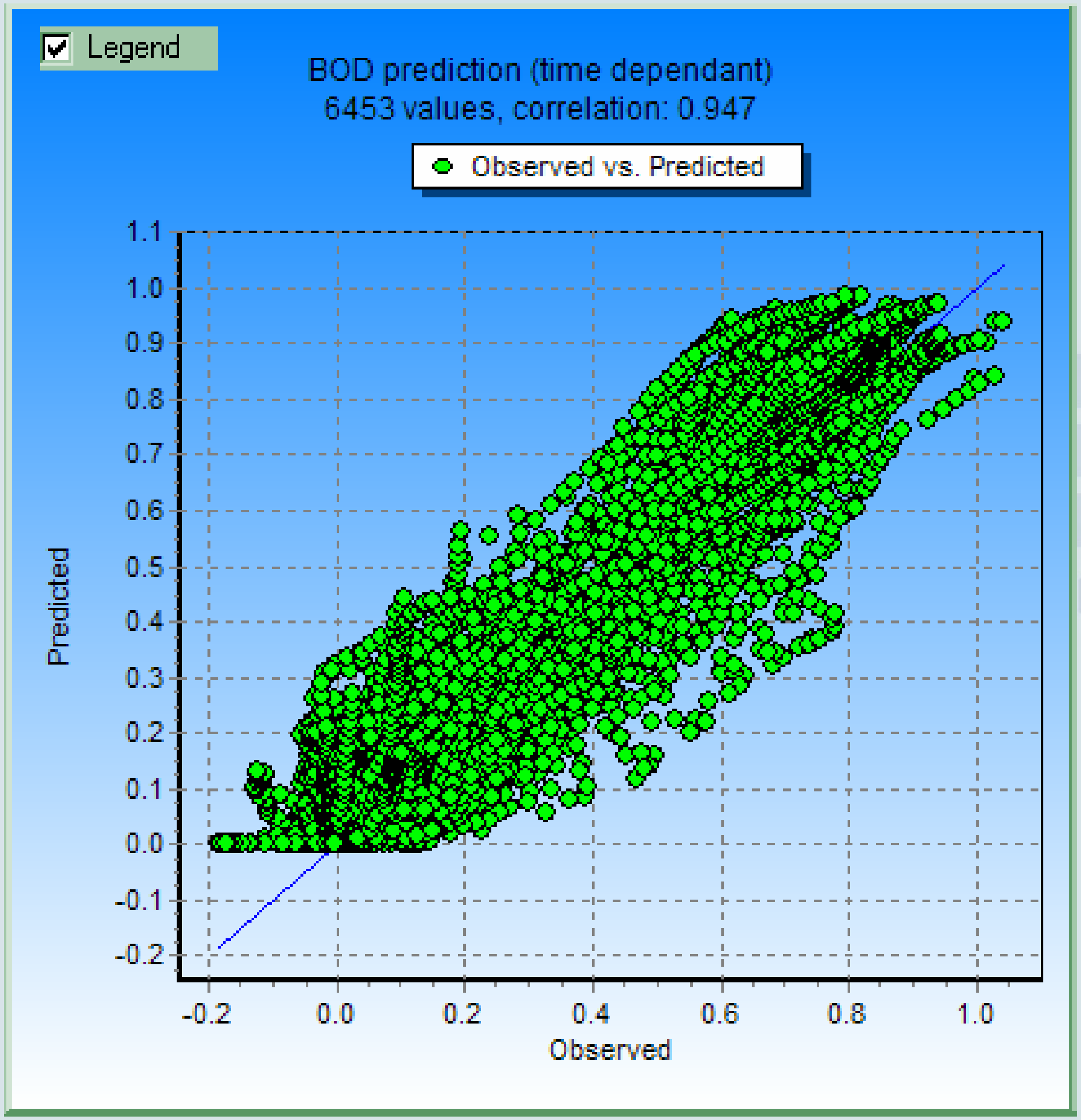
$$P_t = \left(1 - \exp\left(-kt\right)\right)$$

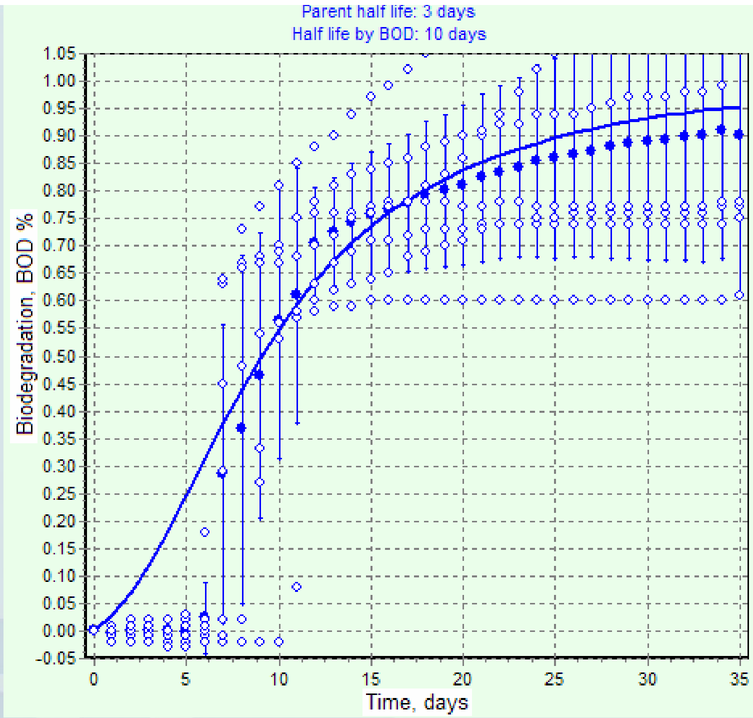
P approximated by second order kinetics

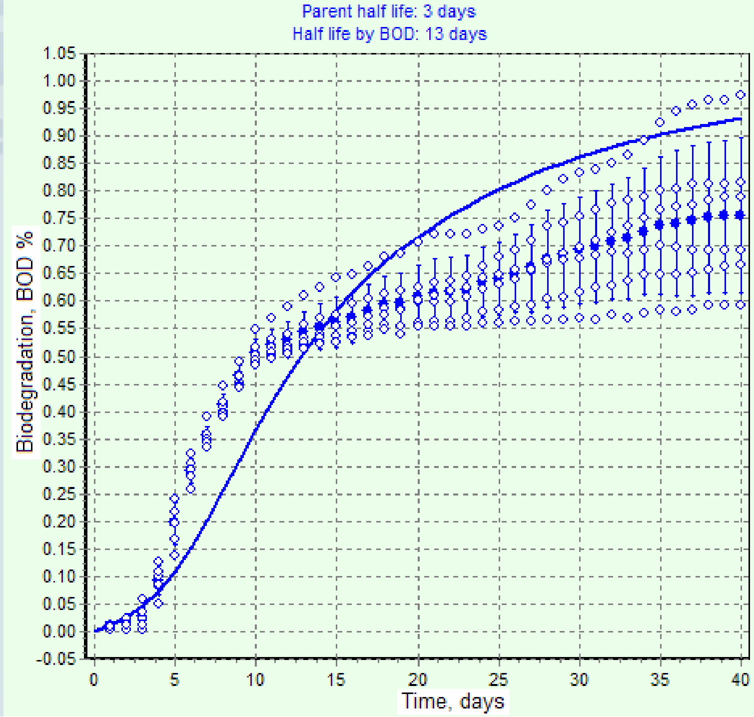
$$P_t = 1 - \frac{1}{1 + kt\left[S\right]_0} =$$

$$= 1 - \frac{1}{1 + k't}$$

CATABOL^{TD} – time dependent model







CATABOL^{TD} – time dependent model

The model is able to predict within OECD 301F test:

1. **Primary half-life – half-life of parent chemical**
2. **Ultimate half-life – half-life by BOD**
3. **Biodegradation at different days**
4. **Metabolites quantity at different days**
5. **Biodegradation within 10 days window**

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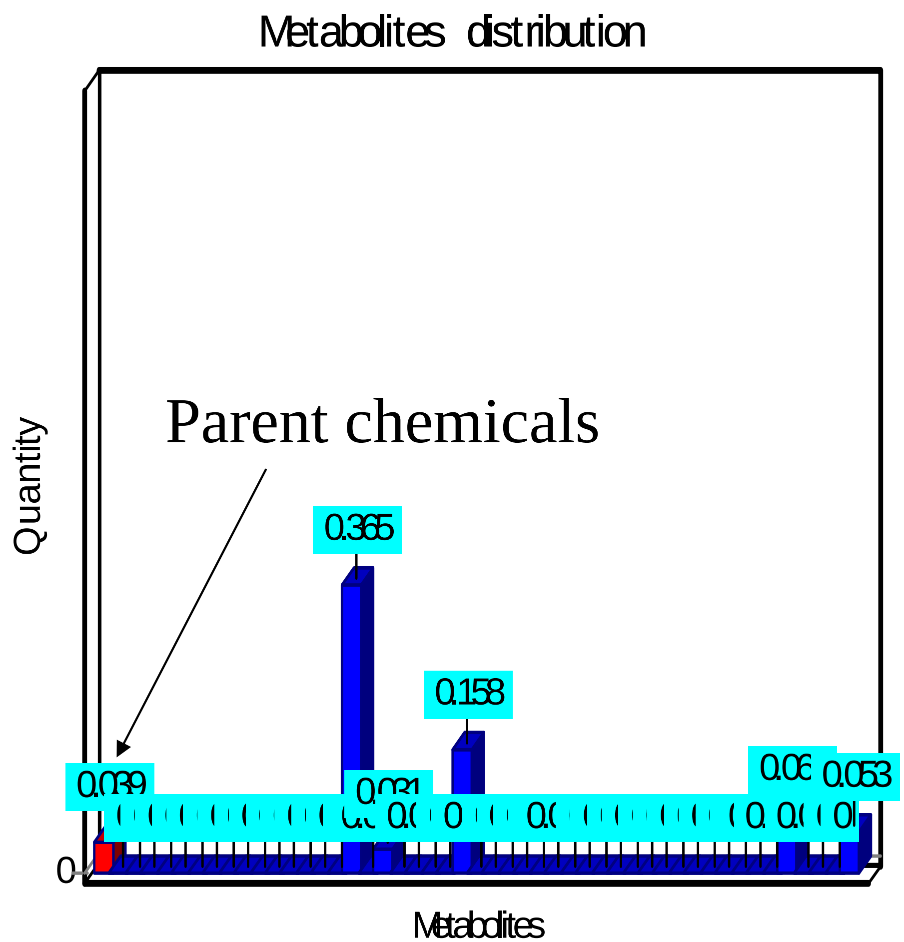
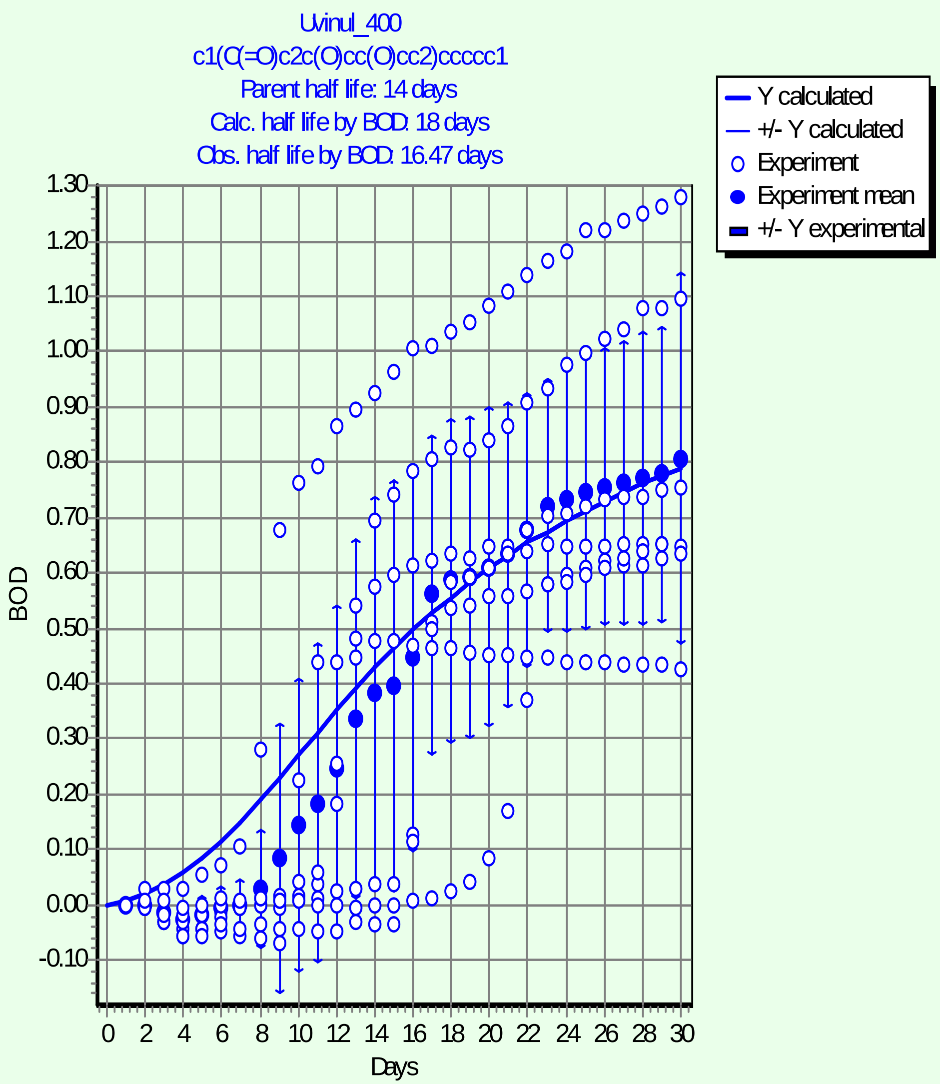
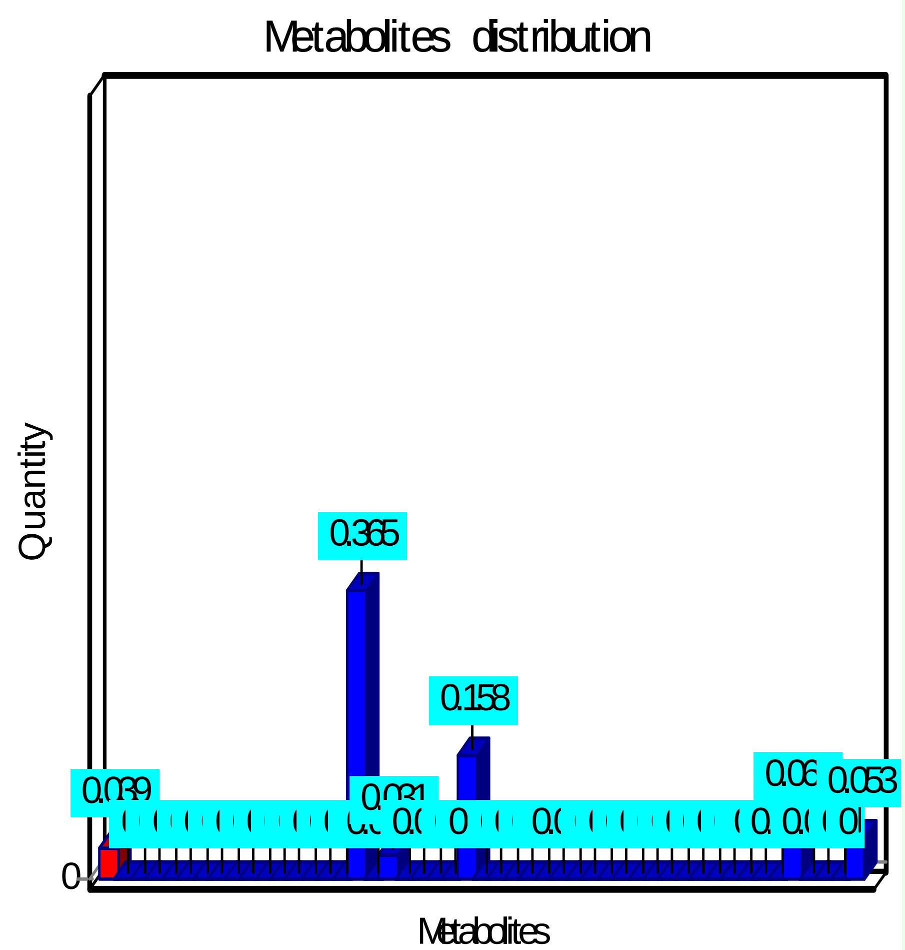


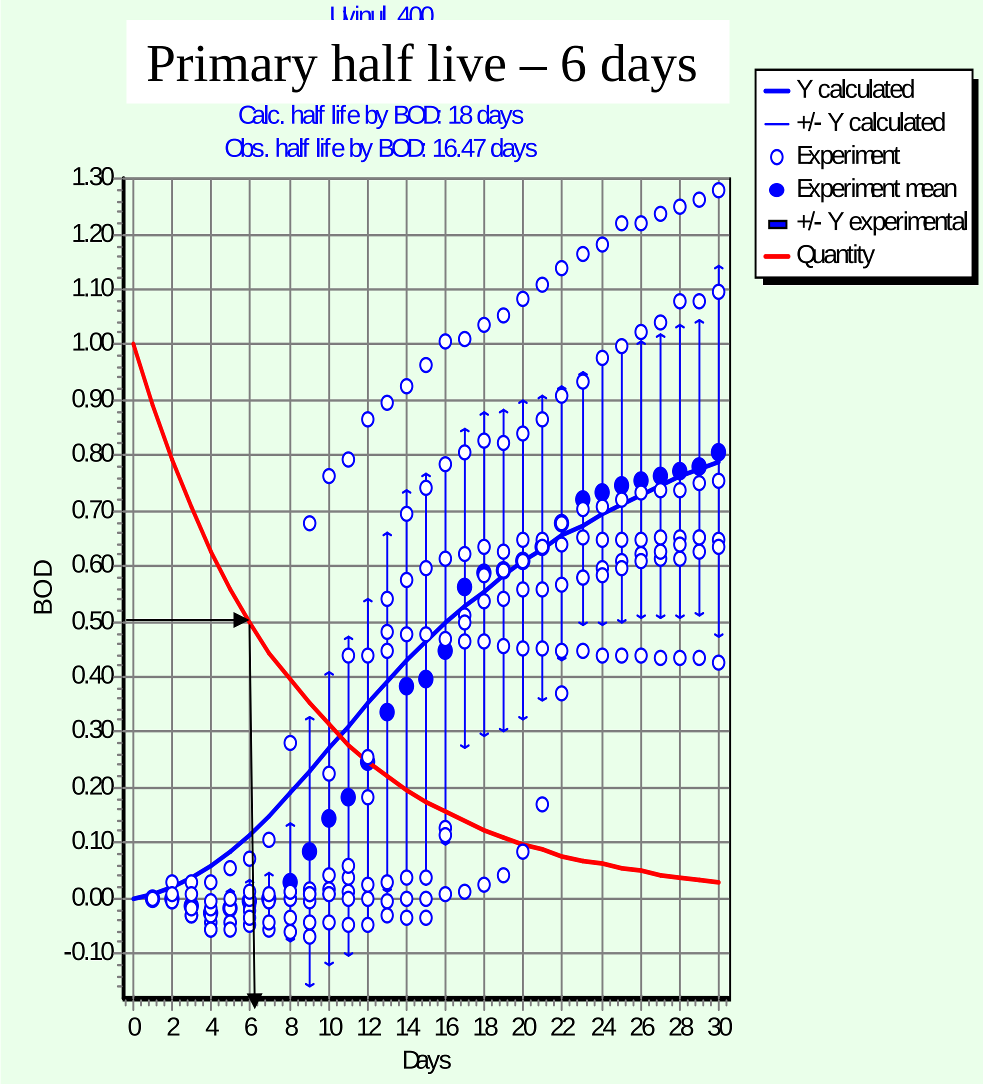
c1(C(=O)c2c(O)cc(O)cc2)ccccc1
Transformation 0, Quantity=0.0386



Primary half live – 6 days



c1(C(=O)c2c(O)cc(O)cc2)ccccc1
Transformation 0, Quantity=0.0386



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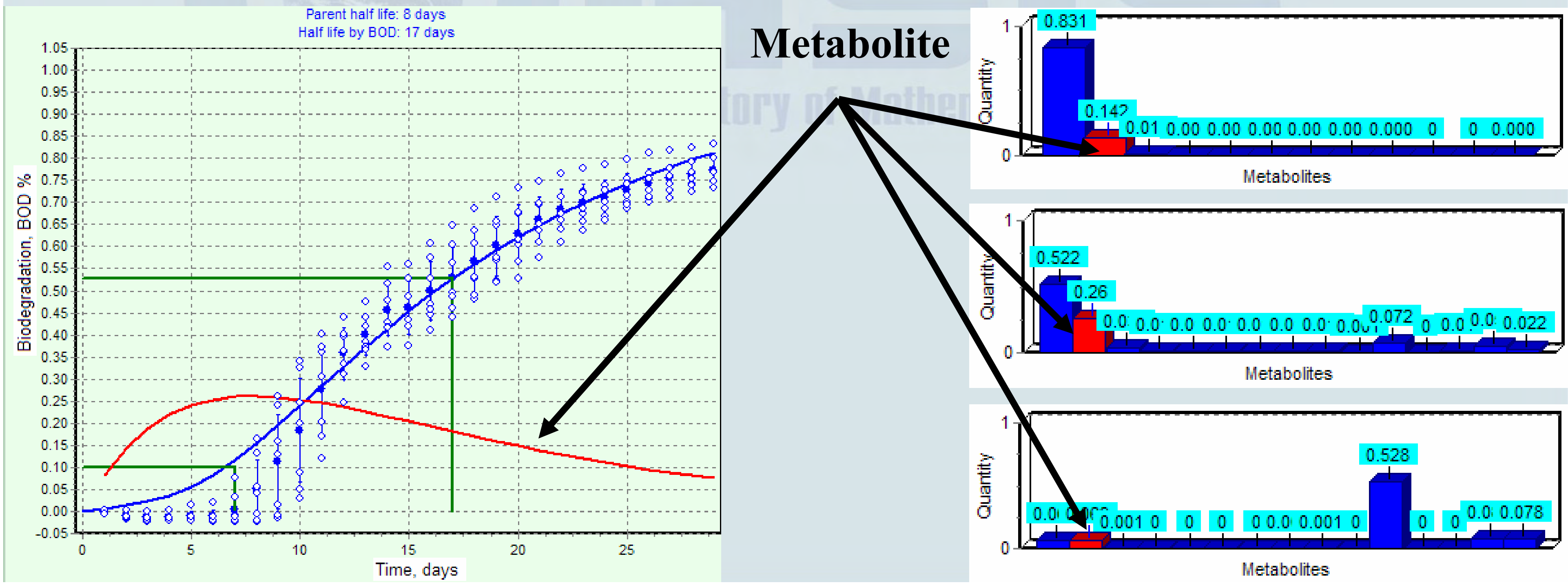

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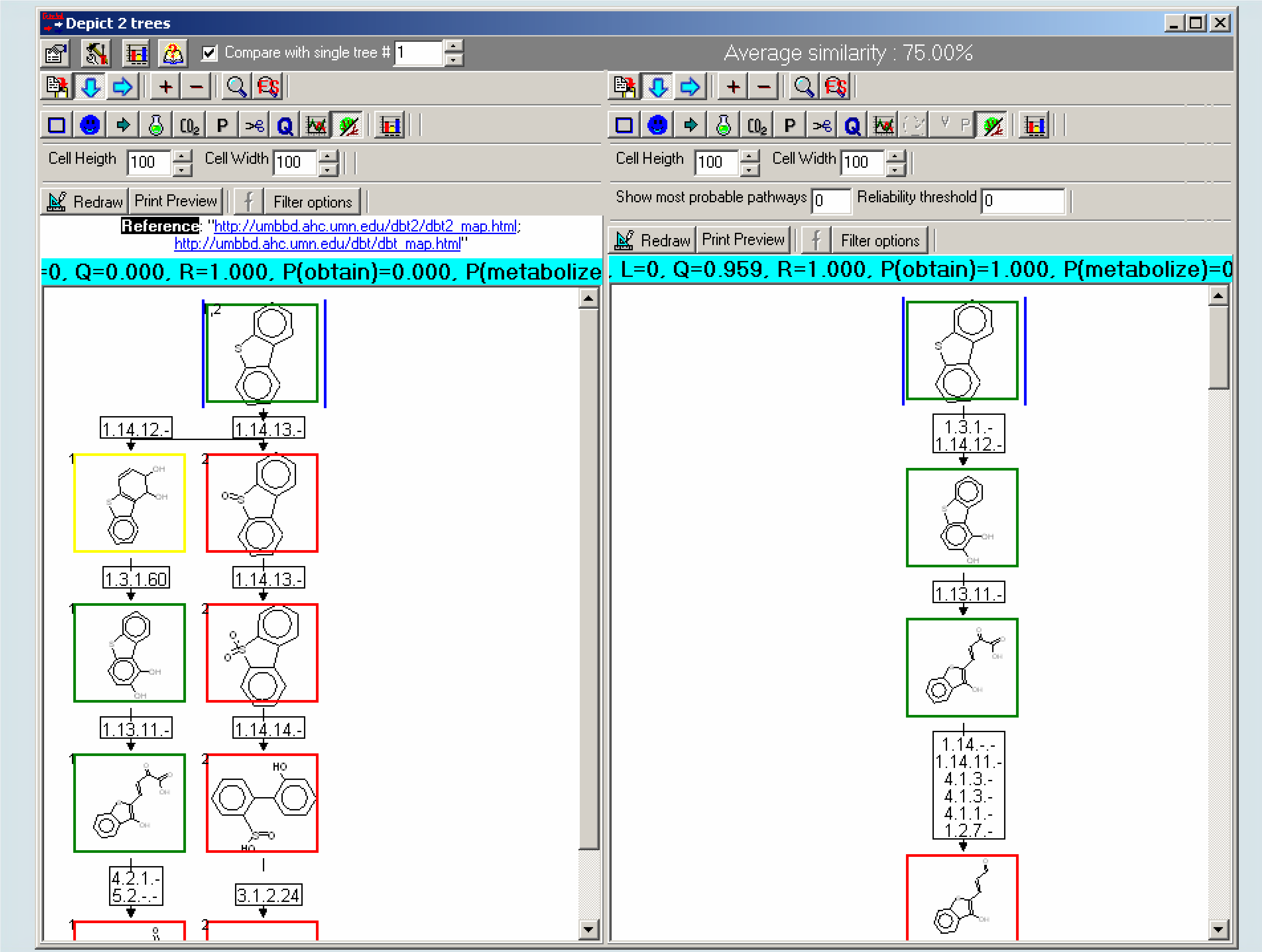
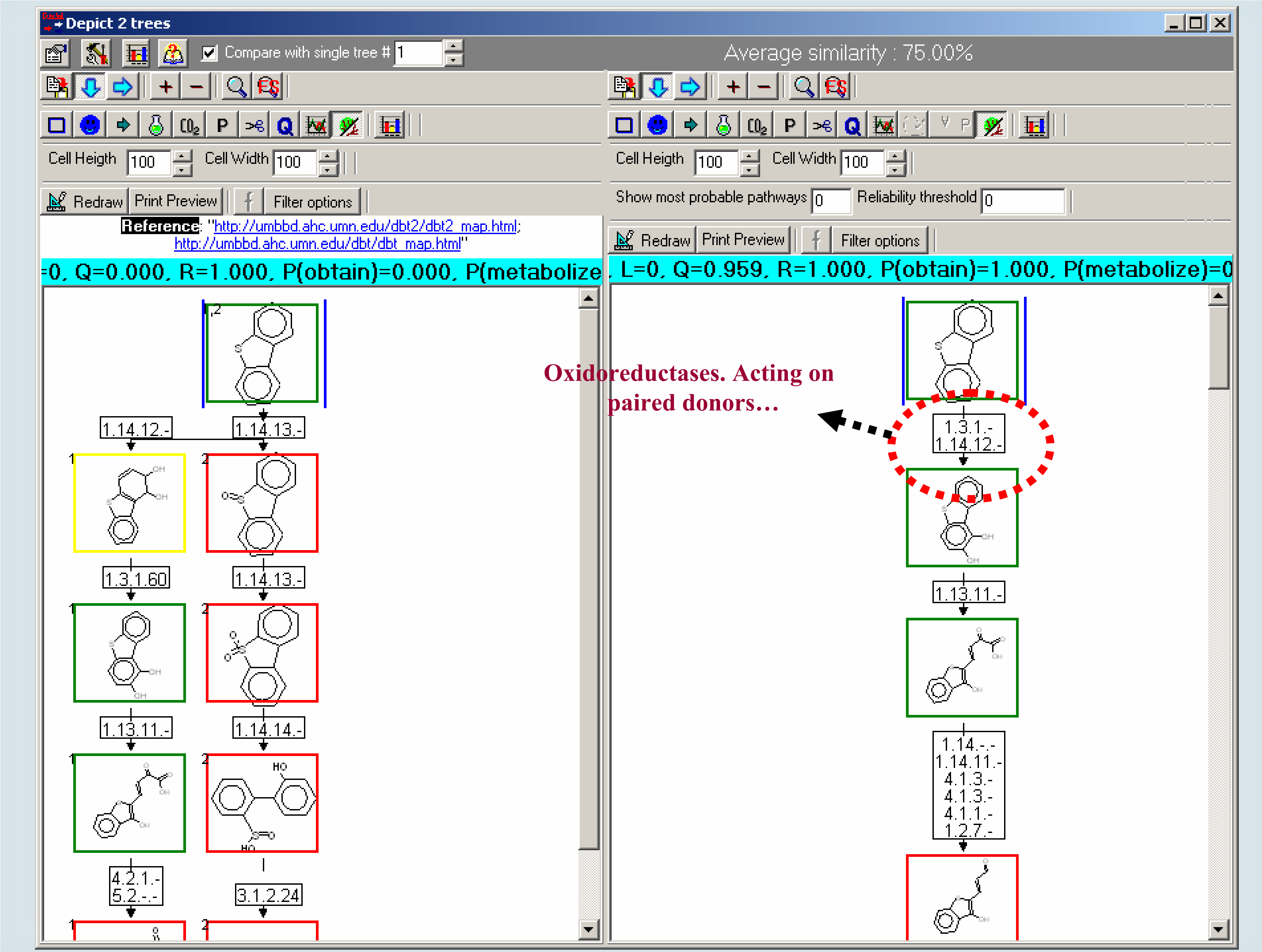
Simulating the effect of gene modification on metabolism

(Microbial degradation)


Depict 2 trees
Compare with single tree # 1
Average similarity : 75.00%
Cell Heigth 100
Cell Width 100
Redraw
Print Preview
Filter options
Show most probable pathways 0
Reliability threshold 0
Reference: "http://umbbd.ahc.umn.edu/dbt2/dbt2_map.html; http://umbbd.ahc.umn.edu/dbt/dbt_map.html"
=0, Q=0.000, R=1.000, P(obtain)=0.000, P(metabolize
L=0, Q=0.959, R=1.000, P(obtain)=1.000, P(metabolize)=0
1.14.12.-
1.14.13.-
1.3.1.60
1.14.13.-
1.13.11.-
1.14.14.-
4.2.1.-
5.2.-.-
3.1.2.24
1.3.1.-
1.14.12.-
1.13.11.-
1.14.-.-
1.14.11.-
4.1.3.-
4.1.3.-
4.1.1.-
1.2.7.-


Depict 2 trees
Compare with single tree # 1
Average similarity : 75.00%
Cell Heigth 100
Cell Width 100
Redraw
Print Preview
Filter options
Reference: "http://umbbd.ahc.umn.edu/dbt2/dbt2_map.html; http://umbbd.ahc.umn.edu/dbt/dbt_map.html"
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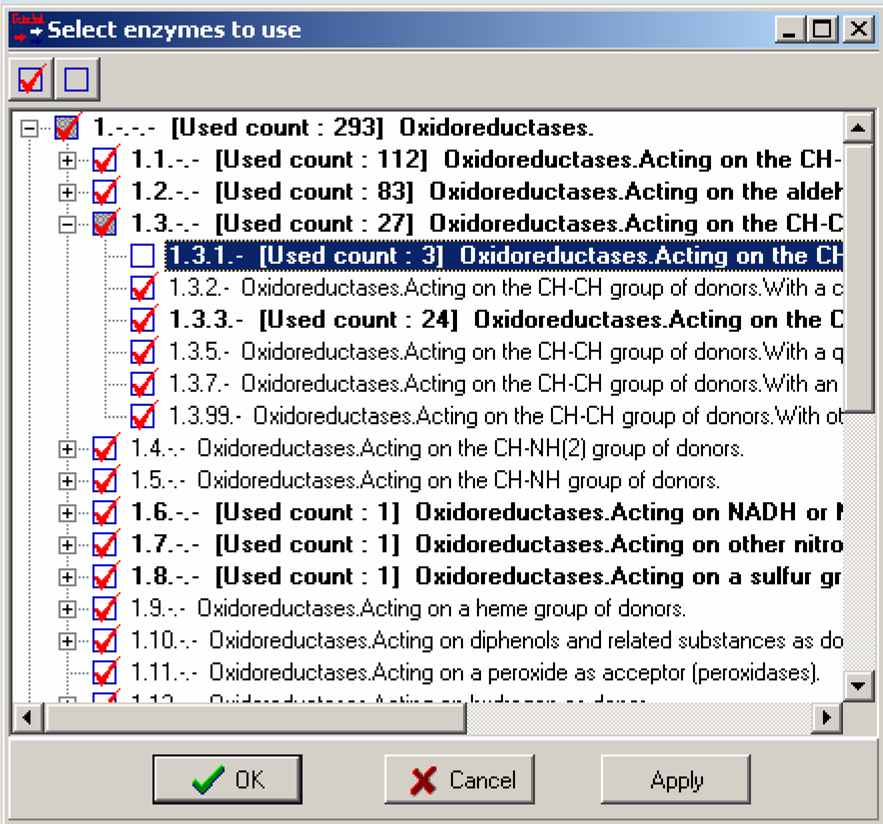
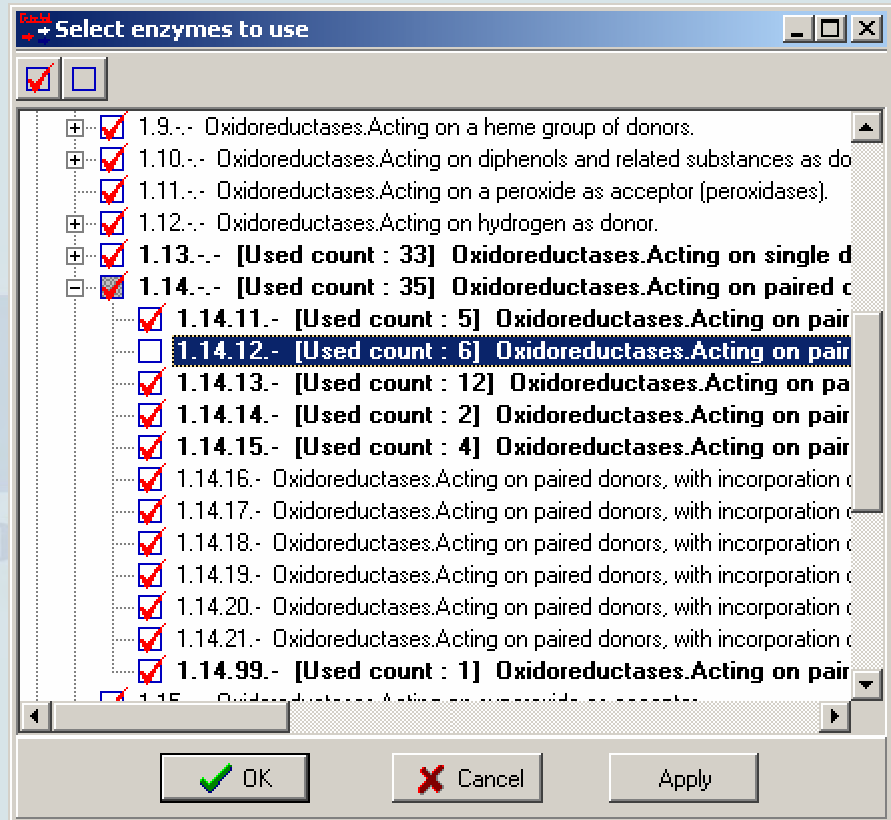
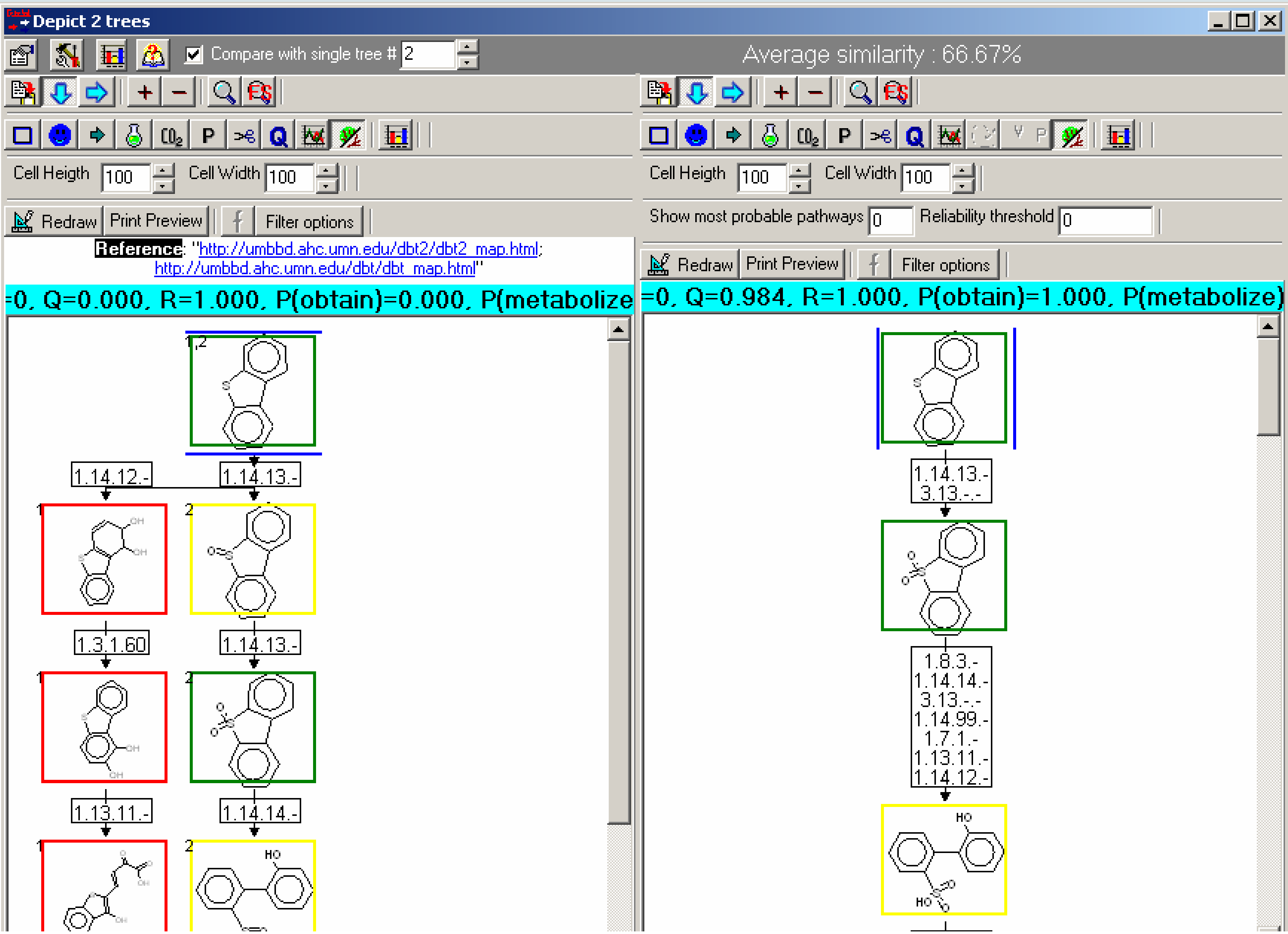
1.14.12.-
1.14.13.-
1.3.1.60
1.14.13.-
1.13.11.-
1.14.14.-
4.2.1.-
5.2.-.-
3.1.2.24
Show most probable pathways 0
Reliability threshold 0
L=0, Q=0.959, R=1.000, P(obtain)=1.000, P(metabolize)=0
1.3.1.-
1.14.12.-
1.13.11.-
1.14.-.-
1.14.11.-
4.1.3.-
4.1.3.-
4.1.1.-
1.2.7.-
Oxidoreductases. Acting on paired donors…

ENZYME MODIFICATIONS IN THE MICROBIAL SYSTEM

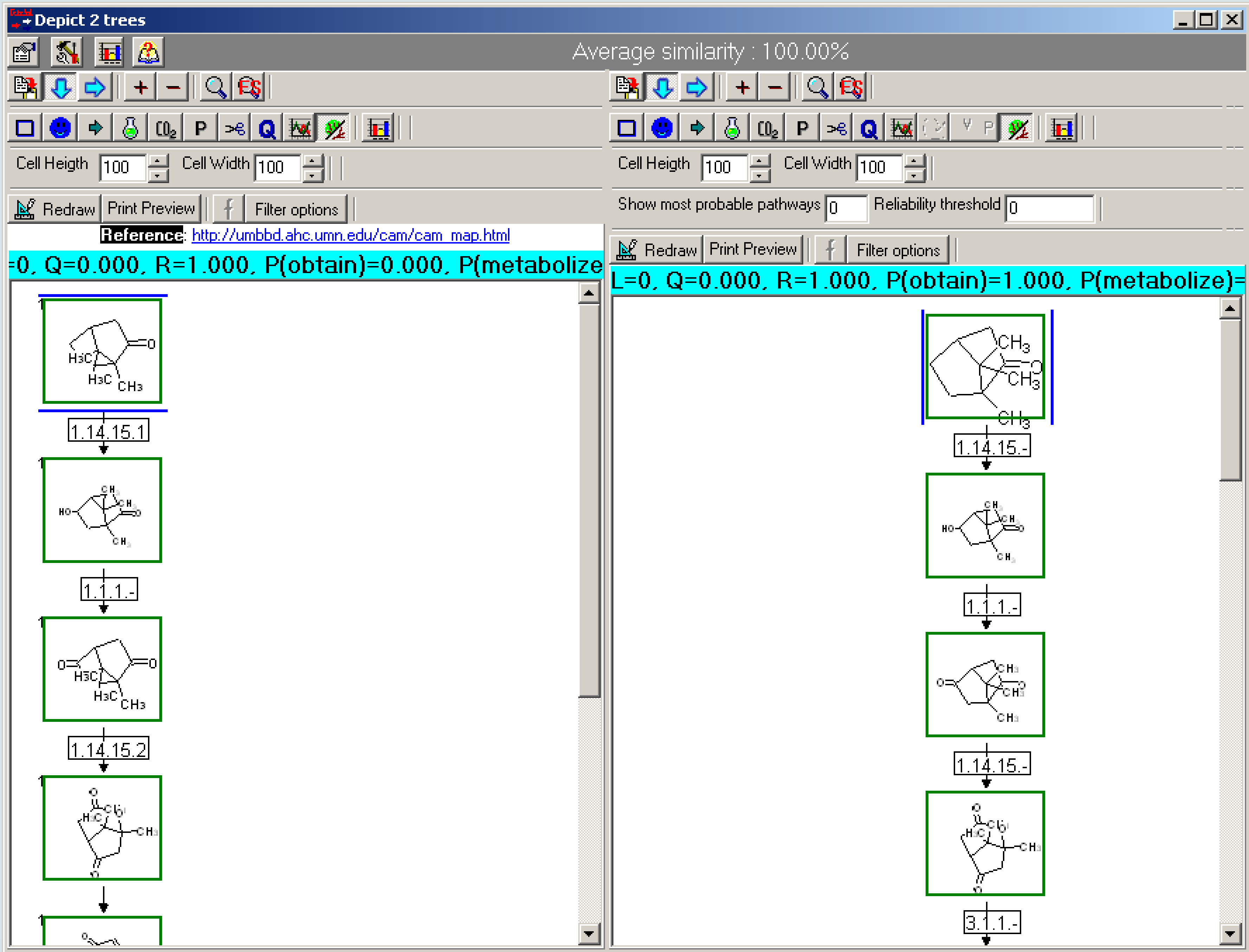




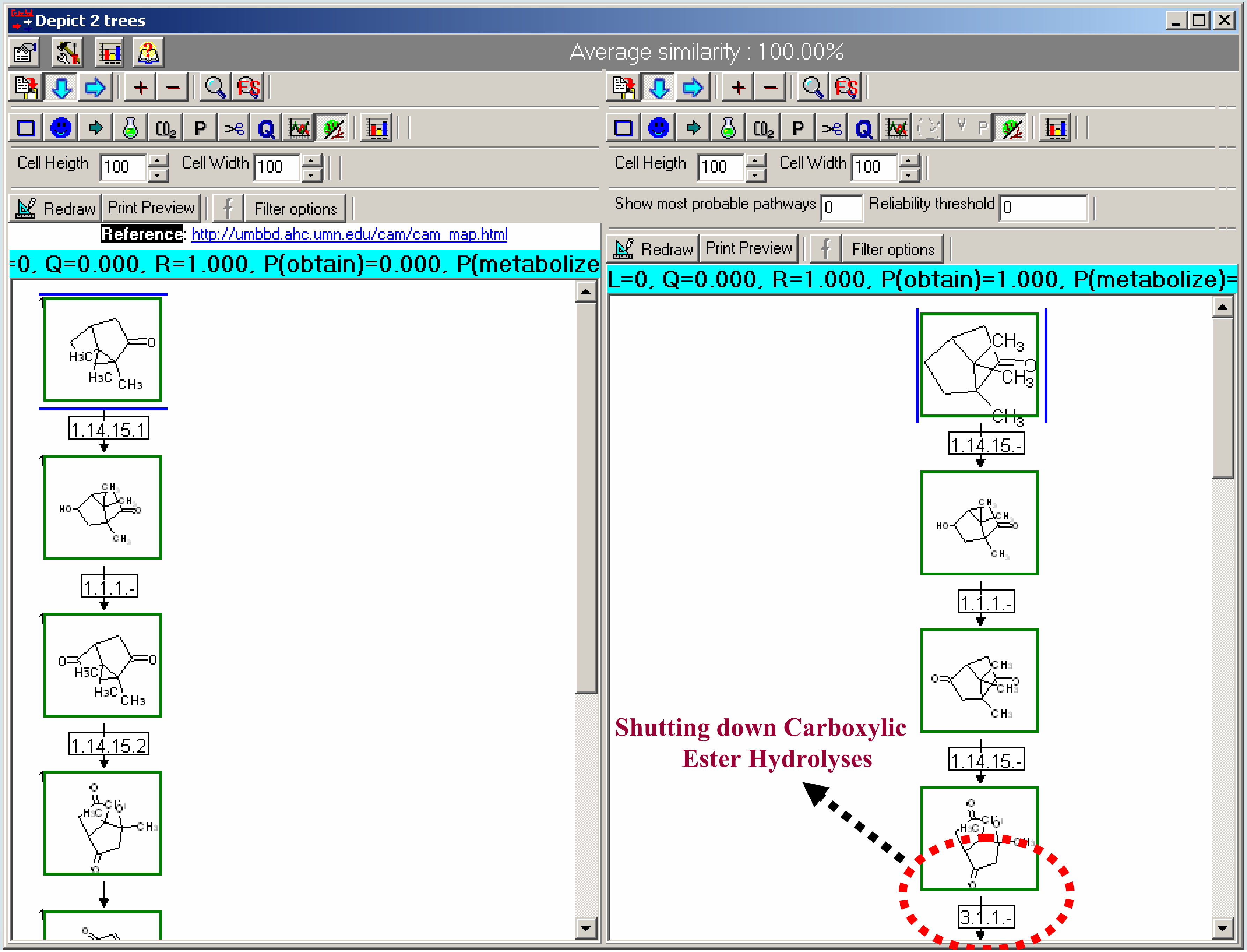
CHANGES IN DEGRADATION PATHWAY DUE TO ENZYME MODIFICATIONS



DEGRADATION OF CAMPHORE – INTACT ENZYME SYSTEM



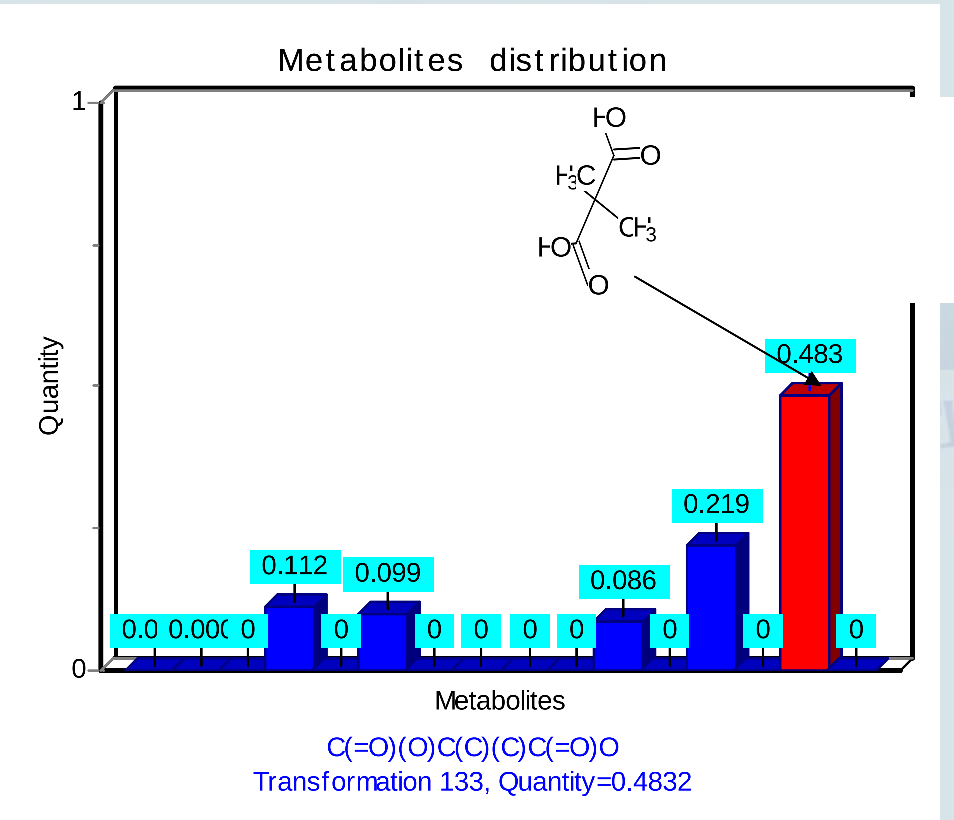
DEGRADATION OF CAMPHORE – INTACT ENZYME SYSTEM

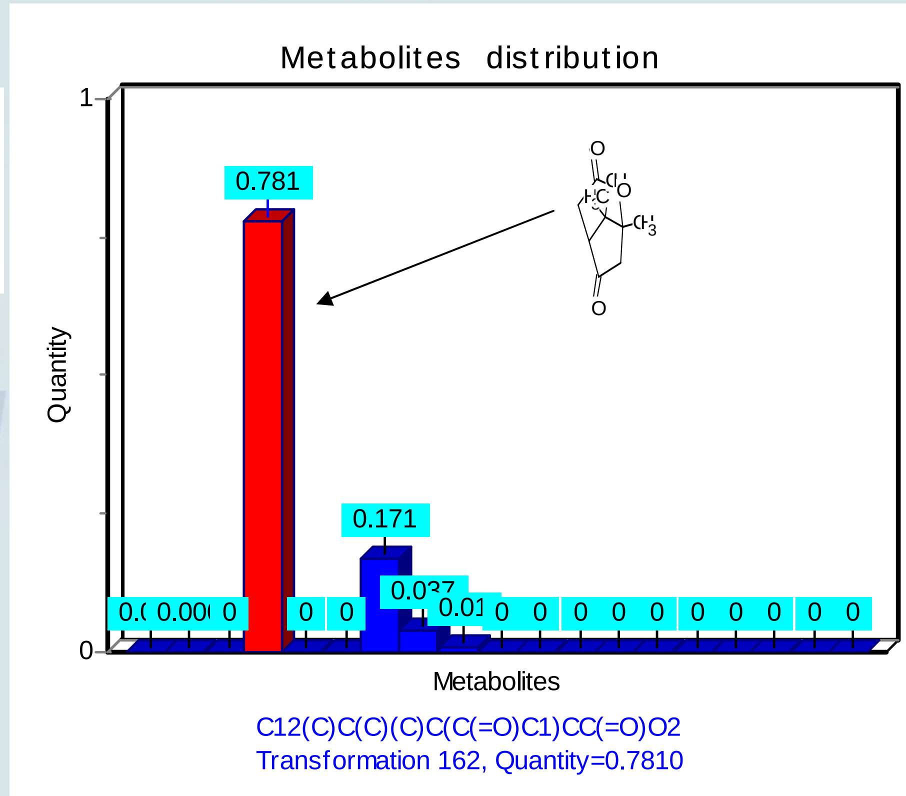


DEGRADATION OF CAMPHORE – ELIMINATING HYDROLAZES IN THE ENZYME SYSTEM

INTACT ENZYME SYSTEM

NO HYDROLASES IN THE ENZYME SYSTEM





Conclusions

- **The advantage of CATABOL is the combination of a knowledge system with a predictive capabilities**

- **For environmental risk assessment, its key value is its ability to show possible metabolites resulting from partial biodegradation that might pose issues in the environment**

- **It's complexity requires interpretation of the results by expert**

Questions & Problems

- MITI (301C) vs. other 301 protocols?
- Single protocol vs. most appropriate one (“best scenario”)
- Effect of bacterial toxicity on biodegradation
- Peer review of biodegradation transformations
- Data consistency and acquisition

Acknowledgements:

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ExxonMobil

Gary Klecka

Dow Chemicals

Markus Gautchi, Jacque Rudieau

Givaudan

EUROPE
BULGARIA
Sofia
Bourgas